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SYNOPSIS OF PATHOLOGY

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BY

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WITH 327 TEXT ILLUSTRATIONS
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TO
D. R. and M. C.

PREFACE TO SECOND EDITION

In revision, an attempt has been made to adhere to principles originally employed, the objective being a concise but comprehensive presentation of pathology. All chapters have had reconsideration, with a view to correcting deficiencies and bringing up to date the text and references. Many changes and additions have been made, too numerous to mention individually, which affect in variable degree nearly every chapter. The number of illustrations has been increased to three hundred twenty-seven, of which seventy-four are new; and four new color plates have been added.

In accordance with the need of the times, greater emphasis has been given throughout to "tropical diseases" and conditions important in "war medicine." The chapters dealing with viral, rickettsial, spirochetel, mycotic, protozoal, and helminthic infections have been enlarged and made more inclusive, and other subjects, such as epidemic hepatitis and blast injuries, have been given attention. The chapters dealing with inflammation, the lung, and the nervous system also have received extensive revision.

The author is again grateful to Dr. Henry Pinkerton for revising the chapter on rickettsial and viral diseases; to Dr. William H. Bauer for assistance with illustrations and for other aid and advice; to Dr. Jeff Minckler, Assistant Professor of Pathology, University of Oregon School of Medicine, for generous aid in revising the chapter on the nervous system; and to Miss Ann Cassady for assistance with the index. The task has been lightened by the help, encouragement, and indulgence of others, which has not been unnoticed, although acknowledgment insufficiently expresses the feeling of appreciation.

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PREFACE TO FIRST EDITION

This volume is intended to fill a gap which has existed between the very elementary manuals of pathology and the abundant excellent larger textbooks and reference works. By the presentation of pathology in a compact and condensed form, it is designed to be useful to the medical student, to the dental student studying general pathology, and to the clinician who must maintain familiarity with the foundation sciences of medical practice.

Modern pathology has a combined base of anatomy, histology, embryology, physiology, biochemistry, and bacteriology and forms an essential linkage with clinical medicine. The difficulties in condensation and simplification of such a subject are fully appreciated. Nevertheless, its very complexity makes more necessary a concise synopsis in which essentials are included, but the broad outlines and patterns of disease are not obscured by a maze of detail. The reactions to injury which constitute disease follow a few well-defined designs. The main features of these should be familiar to every student of medicine and related sciences. Knowledge of the seemingly endless finer details and variations in the patterns of disease will continue to be acquired as long as an individual remains a student of a medical science. The process of learning is most efficiently and pleasurably accomplished by acquiring first the essentials and the broad outlines, with the addition of greater and greater detail as the subject is pursued further, rather than by adding minute fact to minute fact until the required mass is accumulated.

The objectives of this volume preclude bibliographic reference to many authors whose works have been consulted, although indebtedness to them is acknowledged. The references which have been included were chosen because they are reviews, or refer to subjects in which there has been recent interest or advance in knowledge. Recent publications in English in easily available journals have been given preference in the bibliography, in order to facilitate further study of a subject which excites interest.

Numerous friends have made this publication possible by their assistance. The author is particularly indebted to Dr. Henry Pinkerton, Professor of Pathology, Saint Louis University School of Medicine, who contributed the chapter on virus and rickettsial diseases, and freely gave advice con-

cerning other portions of the manuscript. Dr. H. C. Schmeisser, Professor of Pathology and Bacteriology, University of Tennessee College of Medicine, generously allowed the use of many pictures from his large collection of photographs of pathologic specimens. The author's thanks are due also to Dr. William H. Bauer, Professor of Pathology, Saint Louis University School of Dentistry, for much assistance, particularly with the portions dealing with the skeletal system and oral pathology. Dr. J. Minckler gave valuable advice regarding neuropathology. Mr. Hubert R. Teague and Dr. Joseph L. Scianni contributed expert assistance in production of the illustrations. Miss Virginia McCormick and Mrs. R. E. Lazarus especially merit gratitude for their invaluable patient assistance with the manuscript.

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SYNOPSIS OF PATHOLOGY

CHAPTER I

INFLAMMATION, REPAIR, AND REGENERATION

Inflammation is the local reactive change in tissues following injury or irritation. It is a progressive reaction in living tissues, accompanied or followed by reparative or regenerative healing. The agents causing the injury and hence leading to inflammation may be of bacteriologic, physical, chemical, or traumatic nature. The irritant apparently induces direct injury of cells, their resulting altered metabolism liberating materials which initiate the inflammatory process. Inflammation is the most common and fundamental pathologic reaction and in general has a protective action, tending to localize or dispose of the injurious agent, and to set the stage for repairs. In the local area there are vascular effects, disturbances of fluid exchange, and emigration of the white blood cells (leucocytes) into the tissues. The accumulation of fluid and cells is referred to as an exudate. The cells of the local area show some effect of the injury, which may vary from mild degenerative changes up to massive death and destruction. These alterative changes in tissue are essential in the initiation of the vascular, exudative, and reparative changes which follow.

VASCULAR REACTIONS IN ACUTE INFLAMMATION

Following a local acute injury, there occurs a momentary or transitory contraction of vessels, and hence local anemia. This evanescent constriction is rapidly replaced by hyperemia of the part, due mainly to dilatation of capillaries and venules. The increased rate of flow also is transitory and gives way to a slowing of the current in the dilated vessels, which progresses to stagnation and stasis. The local changes in the blood flow are important in that they affect the passage of fluid and leucocytes through the vessel walls, and thus bring about the formation of an exudate. The increased passage of fluid through the vessel walls is due to

elevation of capillary pressure, and increased capillary permeability. According to Menkin¹ there is a permeability factor, **leukotaxine**, a nitrogenous substance liberated by injured tissue, which affects the permeability of the capillary endothelial wall and also causes the migration of polymorphonuclear leucocytes into the injured area. Whether or not histamine is a factor in the increase of permeability attributed to leukotaxine appears to be still in dispute. The slowing of the blood flow in small vessels allows the leucocytes to line up along the vessel walls (margination of leucocytes), instead of being carried in the axial stream. The polymorphonuclear leucocytes pass through the vessel wall and tissue spaces by ameboid motion.

The primary transient vasoconstriction and the early vasodilation are due to nervous factors, perhaps local axon reflexes. The later more severe and prolonged vascular dilatation appears to be a paralysis of vascular walls, influenced by local production of substances injuring small vessels (H-substances, histamine, or histamine-like), by anoxia, or by increase of carbon dioxide. The slowing of the blood current is due to increased viscosity of the blood, and to swelling and irregularity of the endothelial lining of the vessels.

Exudation

The accumulation of an exudate of fluid and cells in the area of injury is dependent on the vascular effects. The fluid (serous) part of the exudate is largely plasma from the blood, and when abundant, may be referred to as inflammatory edema. The fluid coagulates, with the precipitation of an abundant network of fibrin. The inflamed area tends to be walled off, and the injurious agent is localized by the fibrinous material and by thrombotic occlusion of draining lymphatics. When immunity is present, localization of bacterial irritants is aided also by agglutinins, the invading organisms adhering to each other and to the tissues. The early fixation of a bacterial irritant in the area allows time in which leucocytes can assemble for phagocytosis. Polymorphonuclear leucocytes migrate through the vessel walls, attracted to the site of injury by a chemical stimulus, a process referred to as chemotaxis. Leukotaxine may contain a factor concerned in this process. Bacteria, particularly, act as chemotactic agents, intensifying the emigration of neutrophilic leucocytes from blood vessels and directing them toward the injurious agent, leading them to the actual contact with the

foreign particle which makes phagocytosis possible. The mechanism of the directional movement has been thought to depend on changes in surface tension, but McCutcheon² has presented reasons for considering it to be due to a directional orientation of colloidal changes within the cell. Monocytes and lymphocytes have little or no chemotactic activity.

Menkin² has demonstrated an injury factor (necrosin) in inflammatory exudates of animals, associated with the euglobulin fraction, which induces tissue damage and initiates the inflammatory process. The significance of this material in inflammation is not yet fully known. Menkin¹ also has suggested that local changes in hydrogen-ion concentration affect the leucocytes and influence the type of cell found in the exudate. The initial response in acute inflammation is an exudate in which polymorphonuclear leucocytes predominate. The subsequent development of a local acidosis injures these cells, and at a pH of about 6.9 the monocytes (macrophages) tend to survive and predominate. Others⁴ have found that there may be little correlation between the pH and the type of cell in the exudate. In infections with pyogenic organisms, bacterial toxins and enzymes are probably largely responsible for the dissolution of tissues and destruction of leucocytes which result in a purulent exudate and abscess formation.

The action of fibrinous exudate and agglutinins in localization of a bacterial irritant may be opposed by "spreading factors." The effect of these substances, which are believed to include an enzyme (hyaluronidase), is to reduce the viscosity of body fluids, and hence, to promote a free permeation of tissues. Spreading factors are produced by certain invasive bacteria, such as *Cl. welchii* and the pneumococcus. They are also found in testicular tissue, some snake venoms, and in malignant tumors.

The fluid of an exudate usually has a specific gravity of 1.020 or higher, due mainly to an abundant content of serum proteins. Ordinary edema fluid (i.e., a transudate) has a distinctly lower specific gravity. Antibodies of the blood are brought into the tissues with the exudate.

In inflammatory processes there is frequently an increase in the number of circulating leucocytes (leucocytosis). This is stimulated by some globulin-like factor produced in the area which acts on the bone marrow.¹ Fever is also an accompaniment of many inflammations, due to toxic products from bacteria or protein disintegration.

The Cells of Inflammation

Polymorphonuclear Leucocytes.—Neutrophilic leucocytes are the important cells of most acute inflammations. They migrate through the vessel walls and proceed by their ameboid activity to the site of injury, influenced by chemotaxis. Their function is phagocytosis of bacteria and tissue fragments, under the stimulus of opsonins. They disintegrate, and release proteolytic ferments (leucoproteases) which liquefy the injured cells. The leucocytes tend to increase progressively until the irritant is overcome, provided the bone marrow is capable of increased production. Leucocytes are recognized by their segmented or lobulated nucleus. Faintly staining fine granules are present in their cytoplasm.

Lymphocytes.—The lymphocytes are not present in significant numbers in acute inflammatory reactions, except in the nervous system. However, they are numerous and important in many subacute and chronic inflammations. The lymphocytes are rounded cells with a relatively large dark nucleus and very scanty cytoplasm. It has been demonstrated that lymphoblasts when studied in tissue culture have a characteristic type of locomotion and shape which enables their differentiation from other cells which often are morphologically similar (e.g., myeloblasts, monocytes). One function of the lymphocyte appears to be concerned with a reaction to foreign protein.¹¹ Lymphocytes are rarely phagocytic, but it has been maintained by Maximow and others that lymphocytes may be transformed into large mononuclear cells (macrophages) which have an active phagocytic function.¹²

Plasma Cells.—Plasma cells may be present in small numbers in acute and subacute inflammations but are particularly characteristic of chronic inflammation. Plasma cells are slightly larger than lymphocytes, have a basophilic cytoplasm, and an eccentric nucleus in which the chromatin is collected in small masses around the periphery to give it a cart-wheel or clock-face appearance. It has been thought that they are derived from lymphocytes, but they are rarely seen in the circulating blood, and much evidence suggests that they are derived from histiocytic cells, and so are related to monocytes. Little is known of their function, but some evidence suggests that they may be concerned in production of globulin, including antibody globulins.⁹

Eosinophiles.—Eosinophiles have large reddish granules in their cytoplasm, and lobulation of the nucleus is less marked

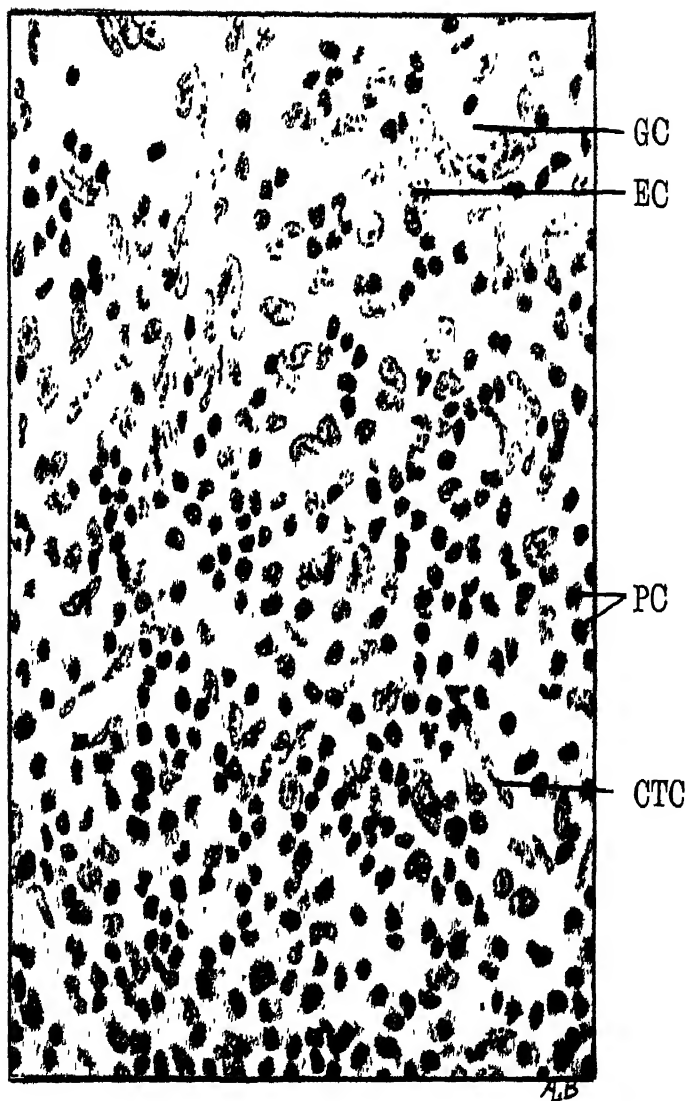


PLATE I.—Chronic inflammatory cells. Study in cell structure to show plasma cells (*PC*); connective tissue cells (*CTC*); giant cells (*GC*), and epithelioid cells (*EC*). (From McCarthy, Lee: *Histopathology of Skin Diseases*, St. Louis, The C. V. Mosby Company, 1931.)

than in the neutrophilic polymorphonuclear leucocytes. Little is known of their function. Though capable of phagocytosis, this does not seem to be a common activity. They are numerous in allergic inflammations of the nose, sinuses, and bronchi (asthma). They also appear as a reaction to certain parasites, especially worms, and may be present in increased numbers in the blood. Subacute and chronic inflammations in the uterus, fallopian tubes, and intestinal tract (especially the appendix) often show numerous eosinophiles.

Basophiles (Mast Cells).—Basophiles are present normally in small numbers in the blood (0.5 per cent) but have little part in inflammatory reactions. It has been suggested, on the basis of similar staining reactions, that they may produce heparin. They have an indented or lobed nucleus, and deeply staining basophilic granules in their cytoplasm.

Macrophages.—These large phagocytic cells are described under a variety of names, being termed monocytes, histiocytes, large mononuclears, polyblasts, endothelial cells, clasmatocytes, etc. They may be derived from monocytes, and perhaps also from lymphocytes, which have wandered from the blood stream into the tissues. The majority of the macrophages, however, arise locally from the cells of the reticulo-endothelial system, both those lining certain vascular spaces and those which are intimately mingled with fibroblasts in nearly all tissues. The corresponding cells in the nervous system are the microglial cells.

Macrophages are large rounded or oval cells, with an oval or indented nucleus, and abundant relatively dense cytoplasm devoid of specific granules. They are highly important in both acute and chronic inflammatory reactions. In acute inflammations they appear later than the polymorphonuclear leucocytes but may persist after the latter have broken down (see pp. 23 and 413). They are actively mobile and highly phagocytic, ingesting bacteria, foreign material, and degenerating leucocytes, red cells, and tissue cells. Thus they act as scavengers and prepare the way for repair. They are the predominant and characteristic cells in certain inflammatory processes, as in typhoid fever, and in tuberculosis where they are transformed into "epithelioid" cells by the waxy material of the capsule of the tubercle bacillus.

Erythrocytes.—Red blood cells appear in the exudate by passage through the excessively permeable vessel walls in the

area of inflammation (diapedesis). In other cases there are small hemorrhages due to rupture of injured vessel walls, so that red cells are more abundant in the exudate. An exudate of hemorrhagic character is present in reactions to certain organisms, such as those of anthrax.



Fig. 1.—Foreign body reaction. Multinucleated giant cells surround particles of foreign material.

Giant Cells.—Multinucleated cells of giant size are generally present when there are materials which resist absorption, e.g., foreign bodies, bone, and are a particular feature of certain inflammatory processes, as in tuberculosis, and foreign body reactions. They appear to be formed by fusion of monocytes around some insoluble material, although nuclear division without cytoplasmic division probably occurs also. The Langhans giant cell of tuberculosis usually has peripheral nuclei, and foreign body giant cells diffuse or central nuclei, but probably they are essentially the same. Other types of giant cells, not concerned with inflammation, are osteoclasts, megakaryocytes, tumor giant cells, and syncytial giant cells found in repair of muscle, nerves, and epithelium.

Phagocytosis

Phagocytosis is the process of ingestion of foreign material or particulate matter. Its importance in the inflammatory reaction and as a defense of the body was first stressed by Metchnikoff. The polymorphonuclear leucocytes and the macrophages are the important phagocytic cells, although a number of other cells exhibit lesser degrees of phagocytic power. The phagocytes are motile and in the case of the polymorphonuclear leucocytes are chemically attracted to the material to be ingested (chemotaxis). The actual mechanism of motility and ingestion probably depends on surface tension changes. The phagocytosis of bacteria is aided by substances present in tissue fluids, such as opsonins and agglutinins. The more highly virulent bacteria tend to resist phagocytosis.

After being engulfed, bacteria, tissue and cell fragments, foreign particles, etc., tend to be digested by cellular enzymes. Not all bacteria are killed by phagocytosis. Some continue to live and even multiply within the phagocytes. This is true of the organisms of tuberculosis, leprosy, gonorrhea, and meningococcal meningitis.

SIGNS OF ACUTE INFLAMMATION

The classical clinical signs of an acute inflammation on the surface of the body, where it can be seen and felt, are swelling, heat, redness, pain, and disturbance of function. The swelling is due to the edema, exudation, and congestion in the area. The inflamed area feels hot in comparison with surrounding areas because the dilated vessels bring a large amount of warm blood to the area, i.e., the heat is only that of the interior of the body. The redness results from the vascular dilatation and congestion. Pain is due to the swelling and tension on tissues caused by the exudate, with pressure on nerves. The cells and tissues involved by inflammation have their normal function disturbed.

TYPES OF INFLAMMATION

Classification of inflammation may be according to (1) duration and severity, as acute, subacute, and chronic; (2) predominant nature of exudate, as serous, fibrinous, hemorrhagic, purulent, and catarrhal; and (3) the causative agent, as tuberculous, syphilitic, staphylococcic, foreign body reaction, allergic, etc. These classifications can often be com-

bined. The ending "itis" is added to the name of an organ or tissue to indicate an inflammatory process, e.g., appendicitis— inflammation of the appendix; hepatitis— inflammation of the liver; dermatitis— inflammation of the skin. The various constituents of exudates often occur combined, so that the reaction may be termed serofibrinous, fibrinopurulent, seromucinous, mucopurulent, etc. The inflammatory reactions induced by specific pathogenic organisms are described in Chaps. IV, V, VI, VII, and VIII.

Acute Inflammation.—The acute inflammations are those which have a rapid course, the lesions clinically exhibiting the classical signs of heat, redness, swelling and pain, or associated with severe or sharp constitutional reactions. Pathologically, the prominent features are vascular changes and exudation of fluid and neutrophiles, but there is insufficient time for development of connective tissue or accumulation of lymphocytes and plasma cells. An acute inflammation may subside, or proceed to subacute or chronic phases.

Subacute Inflammation.—This is considered as a transitional phase between acute and chronic stages. The exudative changes of acute inflammation are still present, while the proliferative changes characteristic of a chronic process have begun. The use of this term probably has but little value except for these cases which cannot clearly be classed as either acute or chronic.

Chronic Inflammation.—Chronic inflammation is a process in which exudative changes are prolonged, and proliferation (especially of connective tissues) forms a prominent feature. It may be simply a late stage of a more acute process, or the inflammation may be essentially chronic (productive) from the beginning. The latter is apt to be the case with organisms of low virulence where their pathogenicity tends to be nearly balanced by the resistance of the body. The predominant cells in chronic inflammation are lymphocytes, plasma cells, and macrophages, although a few polymorphonuclear leucocytes may be present. The proliferative activity, leading to the production of abundant scar tissue, may in itself be distinctly harmful. This is the case in chronic nephritis, where the progressive glomerular scarring eventually results in functional failure of the kidneys.

Serous Inflammation.—Serous exudates, in which there is outpouring of abundant fluid in the inflammatory reaction, occur particularly in acute inflammations of serous cavities. The fluid contains a larger amount of protein and tends to have a higher specific gravity than a transudate. However,

the specific gravity of fluids in serous cavities is not always an accurate guide to their nature.⁵ Fibrin precipitates from the fluid and appears abundantly on the inflamed surfaces. Reactions in other areas, such as some early acute inflammations of the skin, also may have an exudate of predominantly serous nature.

Fibrinous Inflammation.—An abundance of fibrin in an exudate is frequently seen in inflammations of serous surfaces, such as the pericardium and peritoneum. It is also seen in the reaction to diphtheria bacilli, where the fibrin entangles cells and necrotic material to form a false membrane on the surface.

Hemorrhagic Inflammation.—Exudates containing a large proportion of red blood cells so as to have a grossly bloody appearance are usually due to highly virulent organisms which damage small blood vessels. The reactions in severe cases of smallpox, anthrax, meningococcal, and hemolytic streptococcal infections are often hemorrhagic.

Purulent (Suppurative) Inflammation.—Purulent inflammations are those in which there is production of pus, which is a creamy semi-fluid opaque substance containing necrotic material and many polymorphonuclear leucocytes (pus cells), both intact and disintegrating. A suppurative reaction results from a number of injurious agents, mainly bacterial, but also from some chemicals such as turpentine and aleuronat. Bacteria which commonly result in abundant pus production (pyogenic organisms) include staphylococci, gonococci, pyocyaneus bacilli, etc. Suppurative inflammation may be (1) on a surface, (2) localized in the tissues (abscess) or diffusely spreading through tissue spaces (phlegmon or cellulitis).

An abscess is a localized area of pus accumulation. It is found in an acute inflammation in which there is circumscribed destruction of tissue, and collection of many polymorphonuclear leucocytes, which undergo disintegration. Thus a cavity is formed which contains the pus. Abscesses are fluctuant swellings, due to their semi-fluid consistency. Healing is facilitated by drainage and removal of the purulent material; otherwise a relatively slow process of absorption is necessary. Abscesses may become walled off by fibrous tissue, or may spread and extend, and the bacteria gain entrance into the blood stream (pyemia) and form new (metastatic) abscesses in distant tissues. Boils or furuncles are small abscesses of the skin. A carbuncle is a more extensive or spreading abscess of the skin which tends to discharge at several points.

Phlegmonous inflammation (cellulitis) is a suppuration spreading diffusely through tissue spaces. It causes the involved area to be tense, hard, and rigid. Very highly virulent strains of streptococci and other organisms may produce an acute diffuse spreading inflammation without any actual liquefaction and pus production.

Most but not all acute inflammations in which polymorphonuclear leucocytes predominate in the exudate are purulent, i.e., produce pus. A common example in which pus production does not usually occur is pneumococcic (lobar) pneumonia (see p. 356), although leucocytes are abundant in the alveolar exudate.

Catarrhal Inflammation.—Catarrhal inflammation is a superficial and usually mild inflammation of mucous surfaces, in which mucinous material forms a prominent part of the exudate. It is commonly seen in inflammations of the upper respiratory tract and of the large intestine.

Allergic Inflammation.—In allergy there is an alteration or heightening of tissue reactivity (hyperergy) to an antigen. The **Arthus phenomenon** is a marked local allergic inflammation and necrosis which results when an antigen is injected into the skin of an animal previously sensitized to the same antigenic protein. Altered sensitivity or allergy is probably an important factor in many diseases of both bacterial and other origins.¹³ In certain "atopic" conditions, such as asthma and hay fever, hypersensitiveness is the outstanding feature. The most commonly recognized allergic conditions affect the mucosa of the respiratory tract and nasal sinuses, the skin, and the mucosa of the gastrointestinal tract.

In the allergic inflammations of the respiratory tract, such as asthma, one sees hyperplasia and hypersecretory activity of the mucous glands and goblet cells. The tissue is edematous, and eosinophiles form a large and prominent proportion of the inflammatory cells. The basement membrane underlying mucosal epithelium becomes thickened and hyalinized.¹⁴

Granulomatous Inflammation.—A number of infectious agents produce a chronic inflammation characterized by development of focal nodules composed predominantly of mononuclear types of cells, granulation tissue, and fibrous tissue. Multinucleated giant cells are often present. Such lesions are common in tuberculosis, leprosy, syphilis, various mycotic and protozoal infections, and in foreign body reactions.

Foreign Body Reactions.—Foreign materials which are too large to be ingested by phagocytes, become surrounded by macrophages, which fuse to form large multinucleated giant cells. Chronic inflammatory cells and fibroblastic proliferation appear in the surrounding tissue. The foreign material may gradually dissolve or, if indigestible, remains surrounded by giant cells and connective tissue. A foreign body reaction is seen around surgical sutures, cholesterol crystals, waxy materials, ingrowing hairs (e.g., in a pilonidal sinus), talcum powder from a surgeon's gloves in wounds, etc.

REPAIR AND HEALING

A connective tissue reaction is a fundamental part of the response of the body to injury and tends to repair the damage. Whether this reparative process is considered as part of inflammation or as a separate process is immaterial. Proliferative and reparative activity tends to follow the vascular and exudative phenomena of inflammation and often proceeds coincidentally. The final healed state is achieved by development of a connective tissue scar, and by regeneration of destroyed cells. The degree of each and the balance between scarring and regeneration depend primarily on the nature and extent of the destroyed tissue.

The connective tissue cells which react to injury are the fibrocytes and the histiocytes (macrophages). The functions of the latter have already been noted. The changes of repair begin as a proliferation of young connective tissue cells (fibroblasts) and multiplication of small blood vessels, by mitotic division of connective tissue and endothelial cells, respectively. The elongated fibroblasts and buds of endothelial cells grow into and permeate the exudate, producing a highly vascularized, reddish granular mass termed granulation tissue. The granulation tissue replaces the exudate and fills up any gaps in the tissue. This loose and highly vascularized young connective tissue is very resistant to infection. The replacement of necrotic material, exudate, or a thrombus by granulation tissue is referred to as organization.

A large abscess cavity or a tuberculous cavity from which the contents have been discharged may not be filled in by granulation tissue, but rather a fibrous wall forms around it. If, however, the cavity can be collapsed so that the walls are in contact, healing may be completed.

In healing of a surface wound or ulcer, there is proliferation of epithelial cells at the edge, the cells gradually

growing from the periphery to cover over the surface gap. If the area to be covered is too large, the skin edges being more than 1 or 2 cm. apart, the epithelial cells are unable to complete the covering process. Skin graft may be used to supply other foci of epithelial cells from which extension can occur.

When organization is complete and the defect has been filled by granulation tissue, the capillaries decrease in size and number, and largely disappear. The connective tissue shrinks, becomes condensed, develops more collagenous fibers, and acquires the appearance of adult connective tissue. The scar (cicatrix) thus produced is transformed slowly from a soft red area to a pale or white, shrunken, firm fibrous tissue. Shrinkage and contraction may produce deformities of internal organs, or disability if the scar is situated over a joint.

Adhesions of serous surfaces, as between visceral and parietal layers of peritoneum, pleura or pericardium, frequently result from the organization of fibrinous exudates on apposing surfaces. In the pericardium, the effect may be to obliterate the sac and throw an added functional burden on the heart. Adhesions as a result of arthritis may limit the movement of a joint.

The healing of a clean, uninfected incised wound, in which there is little destruction of tissue and where the edges of the wound are held in apposition, occurs with a minimum of granulation and scar tissue, and is referred to as "primary union," or "healing by first intention." If there is much loss of tissue, or infection, the healing process is more delayed ("secondary union") and greater scarring results. In this circumstance the infection must be overcome and the tissue defect filled in by growth of granulation tissue. The granulation tissue must be built up slowly from the bottom and sides of the wound, and epithelium does not grow over the surface until the defect has been filled.

The nature and efficiency of the healing process may be influenced by various factors. The state of nutrition is of importance. Vitamin C is essential for proper collagen formation, and in severe deficiency of this vitamin, wounds fail to heal properly and are easily disrupted. Proper healing of bone is promoted by a sufficiency of vitamins C and D. An adequate protein diet also may be important, as some experiments have indicated that wound healing is delayed when plasma proteins are sufficiently reduced. Complete protection of a wound from any sort of bacterial, mechanical, or chemical irritant delays healing. On the other hand, any-

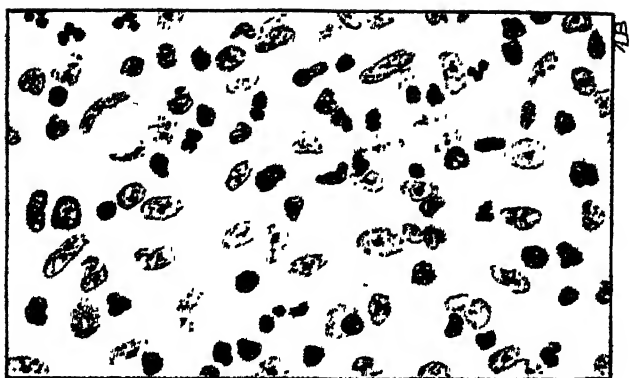


PLATE II.—Granulation tissue and young connective tissue. Upper, Granulation tissue showing various types of inflammatory cells, including neutrophilic polymorphonuclear leucocytes, lymphocytes, plasma cells, and an eosinophile. Lower, Young connective tissue. (From McCarthy, Lee: Histopathology of Skin Diseases, St. Louis, The C. V. Mosby Company, 1931.)



Fig. 2.—Granulation tissue. Note the young capillaries, the elongated fibroblasts, and the sprinkling of inflammatory cells. A fibroblast undergoing mitosis is evident in the central figure.

thing more than a slight injury also delays healing, a circumstance which may result from foreign material or an infection in wounds. Foreign substances vary widely in the type of tissue response which they elicit. Certain metal alloys used to hold fractured bone fragments in position elicit but little tissue response and do not delay healing. Similarly, certain suture materials, such as silk, cotton, and some synthetic fibers, produce relatively little inflammatory response in tissues as compared with other materials, such as catgut. Sulfonamides applied to wounds cause some reaction in tissues, but apparently not sufficient to retard healing seriously.

REGENERATION

Regeneration is the replacement of destroyed tissue by newly formed similar tissue. Physiologic regeneration is the reproduction of tissue lost by the normal wear of life, e.g., of surface epithelium, red blood cells, etc. Regeneration also acts to replace tissues destroyed by disease. Capacity for regeneration decreases as age increases, and also is affected by the state of nutrition of the individual. The most important factor, however, is the type of tissue destroyed. The more highly specialized the tissue, the less is the capacity for regeneration. Thus, connective tissue regenerates most readily, whereas ganglion cells of the central nervous system have no ability to regenerate. The power of various tissues to regenerate may be outlined as follows:

Surface epithelium—marked capacity for regeneration, but in the skin, associated structures, such as hair follicles and sweat glands, do not regenerate, if completely destroyed.

Glandular epithelium—individual cells regenerate, but specialized structures are not so readily formed, e.g., in the kidney, tubular epithelial cells regenerate easily, but whole tubular or glomerular structures are not replaced after their destruction.

Smooth muscle—very little regenerative power.

Myocardium—practically no regeneration, except possibly in infancy.

Striated voluntary muscle—limited capacity for replacement after a destruction of limited size.

Connective tissue—regenerates very readily.

Cartilage—regenerates to some extent from perichondrium.

Bone—regenerates readily from periosteum or endosteum, with preliminary formation of uncalcified osteoid tissue.

Liver—marked capacity for regeneration provided its blood supply and connective tissue framework are intact.

Blood-forming tissues—regenerate readily.

Neuroglial tissue—regenerates quite readily.

Peripheral nerve fibers—regenerate easily if the injured ends are in apposition (see p. 682).

Neurons of the central nervous system—have no power of regeneration.

When tissues without the ability to regenerate are destroyed, repair is by connective tissue, or, in the central nervous system, by neuroglial cells. Even in tissues with good regenerative ability, such as the liver, extensive destruction is repaired largely by connective tissue.

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CHAPTER II

RETROGRADE CHANGES

Among the fundamental results of injury to tissues are the retrograde changes: i.e., atrophy, degeneration, and necrosis (cell death). A wide variety of injurious agents, including bacterial and chemical poisons, trauma, radiant energy, heat, and nutritional disturbances, cause such effects. Retrograde changes may or may not be accompanied by an inflammatory reaction, depending on the degree of damage to the cells, and the rate at which cells die and set free toxic decomposition products.

ATROPHY

Atrophy is a decrease in size of organs, or cells, which were once of mature proportions. This is to be distinguished from **agenesia**, which denotes complete absence of an organ or tissue; **aplasia**, which indicates almost complete failure of development; and **hypoplasia**, which is a failure of full development.

Atrophy of an organ or tissue may be due to a reduction in size or in number of component cells, or to both. When atrophy affects cells, the organ or tissue is usually but not necessarily reduced in size. Frequently the atrophied cells are replaced by connective tissue or fat, which helps to maintain size of the organ. Function is disturbed by atrophy if the reserve capacity of the organ is encroached on.

The general cause of atrophy is inadequate nutrition, which in turn is due to a variety of causes. In certain organs, a normal or **physiologic atrophy** occurs at certain periods of life, as in the thymus at puberty, and in the breast and uterus after the menopause. **Disuse atrophy** occurs in inactive tissues. Such a result is seen in muscles immobilized by splinting or by loss of their motor nerve supply (e.g., infantile paralysis). Glandular organs also atrophy when rendered inactive by occlusion of their ducts (e.g., ligation of the pancreatic ducts results in atrophy of the acini, though the islet tissue remains active). **Starvation** brings about atrophy by using up stored carbohydrate, fat, and eventually protein. A tumor obstructing the esophagus or pylorus may cause starvation, or it may occur without an organic lesion in anorexia nervosa. **Interference with blood supply** causes local atrophy due to insufficient nutrition. This may be

caused by changes in the blood vessels themselves, such as arteriosclerosis. In the aged many organs and tissues become atrophic. Such senile atrophic changes are grossly evident in the skin. Bones become so weakened that they are subject to fracture after slight trauma. **Pressure atrophy** is also dependent mainly on local interference with nutrition. The effects of prolonged and continuous pressure in causing atrophy are seen around expanding tumors and amyloid deposits.

DEGENERATIONS

Cells react to injury by swelling and accumulation in their cytoplasm of substances which normally are invisible, absent, or present only in small amount. The degeneration is named according to the nature of the abnormally accumulated material, as albuminous (cloudy swelling), hydropic, fatty, hyaline, etc. These degenerative changes vary in severity, and usually are reversible. However, severe degenerations may proceed to death of the cells. In one instance, that of amyloid degeneration, the abnormal material accumulates around and between cells, rather than within their cytoplasm.

Cloudy Swelling (albuminous or parenchymatous degeneration).—Most acute infectious and toxic conditions are accompanied by some degree of cloudy swelling. It is the mildest and most common type of degeneration and is easily reversible. It is best seen in the liver and kidneys, and sometimes in the heart. The name is descriptive of the gross appearance. The affected organ is swollen, so that the capsule is tense and the cut surface bulges. The tissue appears more opaque (cloudy) than normal, pale and soft. Microscopically, the affected cells are swollen and have a granular cytoplasm, the granules being of a protein or albuminous nature and due, at least in part, to changes in the mitochondria. The swelling is due mainly to an increased water content of the cytoplasm. The parenchymal cells of the liver and convoluted tubular cells of the kidney show the change most severely. Fresh tissue is essential for recognition, as postmortem autolytic changes are confusing.

Hydropic Degeneration.—While in cloudy swelling there is some imbibition of water into the cell, in hydropic degeneration this is of greater degree. The cytoplasm is markedly swollen, pale, clear and watery in appearance. This type of change is not common, but is seen well in the convoluted tubular cells of the kidney after intravenous administration of hypertonic sucrose solutions.¹ (See p. 301.)

Fatty Degeneration.—Fatty degeneration is the accumulation of stainable fat in cells or organs where normally none is visible. It is a common type of degeneration and indicates a more severe injury than does cloudy swelling. In general, the cause may be said to be anoxemia, whether due to local interference with blood supply, severe generalized anemia, or toxins of bacterial or chemical origin.

Fat is present normally in the body in two states: (1) as visible accumulations in specialized connective tissue cells (adipose tissue) of the omentum, subcutaneous tissue, etc., and (2) in an invisible but chemically extractable form in all organs. This latter type of fat forms an essential component of protoplasm but is not demonstrable by histologic methods. Abnormal fat accumulation may be of two types, corresponding to the above two situations in which fat is present in tissues. Thus in obesity, the fatty accumulation in connective tissue cells may be very great, and it may appear in situations where normally none is seen, e.g., between heart muscle fibers. This is known as **fatty infiltration**, and in the case of the heart it may cause interference with function (see p. 272).

In **fatty degeneration**, stainable fat appears in parenchymatous cells of organs where normally none is visible. Such a change is certain evidence of injury to the cells. It has been considered due to an unmasking or change to a visible form of the fat already present in the cells, a process called **fat phanerosis**. Dible and Davie² have presented evidence that fatty degeneration is usually not such a process of unmasking of fat, but actually an increased accumulation of fat brought from other parts of the body.

Fatty degeneration occurs in a variety of severe infective conditions (e.g., diphtheria), poisons (e.g., by phosphorus or arsenic), and in severe generalized anemias (e.g., pernicious anemia). The liver, heart, and kidneys are most frequently affected. A fatty liver is swollen, soft, pale and has a yellowish tinge and greasy feel. The original distinction between fatty infiltration and fatty degeneration in the liver, judged on the size of the fat droplets in the liver cells, has been abandoned. Fine droplets were believed to indicate fatty degeneration, but fatty change in the liver is almost always a fatty infiltration in the sense that the fat is brought from elsewhere. The liver is important in the metabolism of fat, and accumulation there may result from either excessive mobilization or defective utilization. Starvation and chronic alcoholism lead to excessive mobilization of fat in

the liver. In experimental animals, choline deficiency causes marked fatty infiltration of the liver. The anoxemia of chronic passive congestion often causes fatty change around central vein areas.

In the heart fatty degeneration may be patchy or diffuse. Severe anemias are apt to cause the patchy form, seen especially well on the interior of the ventricles, which are flecked and mottled by yellowish bands and striations, producing a thrush-breast appearance. A diffuse fatty degeneration may result from severe toxic or infective states. The whole heart is very flabby, pale, and greasy when the condition is severe, but lesser degrees are detected only microscopically and by the aid of fat stains.

The fatty kidney is large, and pale or white. The fat is most prominent in the epithelial cells of convoluted tubules. Such fatty change occurs in subacute nephritis and in the variant known as lipoid nephrosis (see p. 300).

Fatty degeneration occurs in sheaths of nerve fibers distal to a point of section (Wallerian degeneration—see p. 682).

Fat may also appear in phagocytic cells around an area where disintegration of tissue has caused the setting free of fat. This is particularly well seen around infarcts of the brain. Fatty tissue occasionally replaces destroyed parenchymatous tissue, e.g., in the kidney. Fatty substances introduced into the lung are taken up by phagocytic cells and cause an inflammatory reaction (lipoid pneumonia, see p. 362).

For methods of histologic demonstration of fat, see Table I. In preparation of ordinary paraffin sections, fat is dissolved out by alcohol or other reagents, leaving a clear area or vacuole.

Hyaline Degeneration.—Hyaline is a term used for translucent, homogeneous, structureless materials which stain with eosin. There are a variety of hyaline materials, mainly of protein nature, which may be of either epithelial or connective tissue origin. Certain types of hyaline, such as amyloid, have distinctive characteristics or staining reactions and hence are separable from the general group.

The most common type of hyaline is formed from connective tissue and is evident in any dense scar tissue. Marked hyaline thickening of the pleura may follow chronic inflammation, and hyaline thickening of the splenic capsule is also common. Arteriosclerotic lesions of blood vessels often show hyalinization as a prominent feature. Hyaline formation is also common in certain tumors, such as fibromyomas of the uterus.

TABLE I
COMMONLY USED TISSUE STAINS

USE	STAIN	COMMENT
Routine histologic study	Hematoxylin and eosin	
Connective tissue	Azocarmine	Connective tissue stains deep blue. Valuable for study of renal glomerular basement membrane
	Mallory's aniline blue Masson's trichrome Van Gieson	Connective tissue stains blue Connective tissue stains blue Collagen fibers stain red— muscle fibers stain yellow —differentiates connective tissue and muscle fibers
Elastic tissue	Verhoeff's stain	Elastic fibers stain black
Reticulin	Ammoniacal silver impregnation	Reticulin fibers stain black
Fibrin	Weigert's modified Gram stain	Fibrin stains blue
Amyloid	Congo red Methyl violet	Amyloid stains red Amyloid stains red
Glycogen	Best's carmine	Glycogen stains red. Requires fixation in absolute alcohol
Mucin	Mayer's	Mucin is stained red
Fat	Scharlach R (scarlet red) and Sudan III	Neutral fats and lipoids stain orange to red. Used on frozen sections (stains mineral oil)
	Osmic acid	Fat stains black (does not stain mineral oil)
Gram-positive bacteria	Gram's stain for paraffin sections	
Gram-negative bacteria	Methylene blue	
Bacteria	Giemsa's stain (Wolbach's modification)	
Acid-fast bacteria (tubercle bacilli and lepra bacilli)	Ziehl-Neelsen's stain	Acid-fast organisms are stained red
Spirochetes	Levaditi's silver impregnation method	Spirochetes appear black
Free iron	Potassium ferrocyanide (Prussian blue stain)	Hemosiderin pigment stains blue
Calcium	Van Kossa's silver method	Calcium appears black

A different type of hyaline degeneration is that in which fine droplets of eosin-staining material appear in the cytoplasm of epithelial cells. Such hyaline droplet degeneration is not uncommon in the convoluted tubules of the kidney and indicates severe injury. Hyaline masses also appear in the liver cells in portal cirrhosis, and in the basophiles of the pituitary in Cushing's syndrome.

Zenker's (Waxy) Degeneration.—Hyaline changes in voluntary muscle were described by Zenker in fatal cases of typhoid fever, and are also seen in other severe infections, such as pneumonia, the degree paralleling the intensity of the infection. Bacterial toxins or excess accumulation of lactic acid is probably responsible for the change, rather than localization of the infection in the muscle. The lesion is best seen in the rectus abdominis. The muscle is very pale and friable, so that rupture of the fibers and small hemorrhages are frequent. Microscopically, the affected fibers have lost their striations and have a hyaline appearance.³

Amyloid Degeneration.—Amyloid is a hyaline material characterized by deposition in intercellular spaces around cells rather than in cells, and by specific staining reactions with iodine, methyl violet, and Congo red. It is insoluble in water, slightly soluble in strong acids and readily soluble in strong alkalis. The exact chemical composition is unknown, but protein fractions and a sulfate-bearing polysaccharide have been identified.⁴ The disappearance of Congo red from the blood one hour after intravenous injection is a useful clinical test for amyloidosis.⁵

Amyloid deposition is associated with long-continued, infective, tissue-destructive processes, such as tuberculosis, leprosy, osteomyelitis, etc. Exact causative factors in amyloidosis are still unknown. The organs most frequently involved are spleen, kidneys, liver, and adrenals. Blood vessel walls tend to be affected first and most prominently in these organs.

The amyloid spleen is enlarged, firm, and of rubbery or elastic consistency. On the cut surface the amyloid areas have a characteristic pale translucent appearance. The involvement may be focal or diffuse. In the **focal form** (sago spleen) the deposition is in arteriolar walls and extends into surrounding lymph follicles. The involved foci are prominently pale and translucent against the red background of the remainder of the spleen. In the **diffuse form** there is widespread deposition between the fibrous reticulum of the spleen, the follicles tending to be spared. . .

In the liver, marked amyloid deposition causes it to be enlarged, firm, and unusually translucent. Deposition tends to occur first in the mid-zonal region of the liver lobule, appearing in the space between the sinus endothelium and the liver cells. In the liver, as elsewhere, the deposition of amyloid tends to cause pressure atrophy of the parenchymatous cells.

Amyloid disease of the kidney is occasionally severe enough to disturb renal function and give a picture of renal disease. Amyloid is deposited chiefly in glomeruli and blood vessel walls. In the glomeruli, the amyloid is deposited between the basement membrane and endothelial lining of the capillaries. The capillaries are narrowed and finally obliterated so that the glomerulus becomes functionless and secondary changes develop in the tubules.

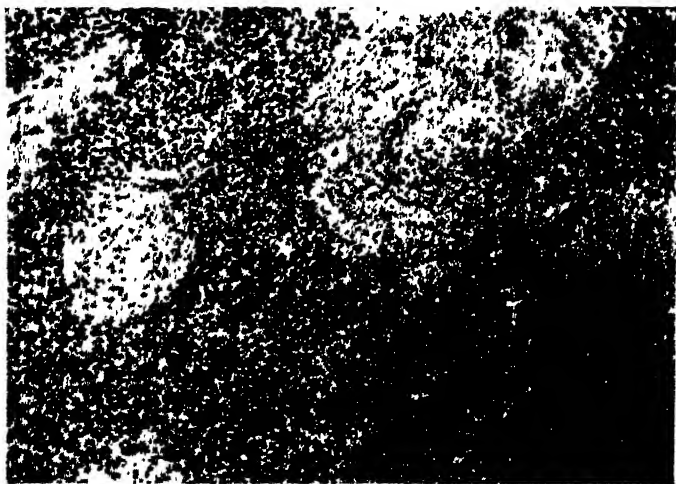


Fig. 3.—Amyloid in the spleen.

Primary systemic amyloidosis also occurs but is rare. Mesenchymal rather than parenchymatous tissues tend to be involved. Amyloid may be deposited in irregular masses, or in the form of "rings" in fatty tissue. Foreign body giant cells and lymphocytic infiltration occasionally occur in relation to the amyloid masses⁶ in primary amyloidosis, but not in the common or secondary type of amyloidosis.

Mucinous Degeneration.—Mucin is a clear structureless material which stains lightly with basic dyes (hematoxylin). In certain epithelial tumors and in some catarrhal inflammations of mucous membranes, an excess is secreted by the epithelial cells. When masses of mucinous material are so formed, it is often referred to as mucinous degeneration. A somewhat similar (muroid or myxomatous) material may be formed by connective tissue, and is found in the subcutaneous tissue in thyroid deficiency (myxedema) and in the connective tissue tumors called myxomas.



Fig. 4.—Hydropic degeneration of the kidney. Diethylene glycol poisoning. Note the swollen tubular cells with water-clear cytoplasm. (South. M. J. 34: 257, 1941.)

Calcareous Degeneration.—Calcium salts tend to precipitate in degenerated, dying, or dead tissue (dystrophic calcification), apparently influenced by a local relative alkalinity. Metastatic calcification occurs in conditions of disturbed calcium metabolism, such as hyperparathyroidism and hypervitaminosis D (see pp. 195 and 540), and affects blood vessels and kidneys most commonly.

NECROSIS

The most serious effect of injury is death, which may be of the body as a whole (somatic death), or of localized areas of tissue or certain cells. Cell or tissue death within the living body is termed **necrosis**, and is recognizable by the changes which the dead tissues and cells undergo after their death. The severe degenerative changes which eventually terminate in death of the cells are referred to as **necrobiosis**.

Necrosis may be caused by almost any type of severe injury. Macroscopic areas of dead tissue tend to be opaque, i.e., the normal translucency of most living tissues is lost, and a whitish or yellowish color is assumed. However, gross appearances of necrotic tissue may differ, varying with the type of tissue affected and the causative agent, so that several types are described.

Coagulation necrosis is a type commonly produced by cutting off of blood supply, i.e., in infarction, and is characterized by a protoplasmic coagulative process. In such necrosis general architectural features may be preserved for a considerable period, although cellular detail is lost. **Caseous necrosis** is so called because of a cheesy macroscopic appearance. It is particularly characteristic of the necrotic tissue resulting from tuberculous infection. Microscopically, the architectural outline of the necrotic tissue is completely lost. **Gummatous necrosis** which results from syphilis resembles caseous necrosis microscopically, but in the gross has a more rubbery consistency. In **liquefactive necrosis** the dead area softens and eventually liquefies. It is especially characteristic of necrosis in the central nervous system. It may follow other types of necrosis in other tissues, and the term may be applied to the liquefaction of pus in abscesses.

Microscopic recognition of necrosis is aided by nuclear changes in necrotic cells. The nucleus may shrink and stain more intensely basophilic (pyknosis), or may fragment (karyorrhexis). More commonly the nucleus simply loses its ability to stain differentially with basic dyes (karyolysis) so that it fades and eventually is indistinguishable. Necrotic tissues tend to stain diffusely with red acid dyes such as eosin, with lack of any blue or hematoxylin-staining material. Any calcium which precipitates in the necrotic material stains with hematoxylin, thus appearing as bluish masses.

Fat necrosis is most commonly the result of pancreatic disease, which allows release of enzymes which act on fat. The fat of the pancreas, omentum, or other intra-abdominal

tissues shows whitish opaque nodules of very characteristic appearance. A zone of congestion and leucocytes surrounds the necrotic area. Eventually, calcium tends to be deposited in these areas, and a foreign body reaction occurs around them. Fat necrosis may also occur in the breast and other subcutaneous areas, from trauma, toxic agents, circulatory disturbances, and injections. There is necrosis of the fat cells, with release of neutral fat into tissues and its subsequent change into fatty acids or soaps. An inflammatory reaction occurs, often of foreign body type with formation of giant cells, and a tumor-like mass may result.

Gangrene.—Gangrene is a massive necrosis of tissue, to which there is usually added an invasion by saprophytic bacteria. Distinction is often made between dry and moist gangrene. **Dry gangrene** (or mummification) is a term usually applied to ischemic necrosis of a portion of an extremity, i.e., an infarction of the extremity. The tissue becomes dried out, greenish yellow, and finally dark brown or black. Inflammatory reaction in the adjacent living tissue causes a sharp line of demarcation separating healthy and dead tissues. In **moist gangrene**, which may be found in almost any part of the body, saprophytic organisms invade the dead tissue through wounds or from the respiratory or intestinal tract, causing putrefactive changes. **Gas gangrene** occurs when the invading saprophytes are of the gas-forming group (e.g., the Welch bacillus).

Senile gangrene is a necrosis in an extremity due to interference with blood supply by arteriosclerosis. It is often a dry type, but may be moist and putrefactive. **Diabetic gangrene** is similar, and also due to arteriosclerosis, but tends to occur at an earlier age. Gangrenous extremities due to interference with blood supply may also be due to Raynaud's disease (vascular spasm), ergot poisoning (vascular spasm), and thromboangiitis obliterans (endarteritis).

POST-MORTEM CHANGES

Somatic death, or death of the body as a whole, is followed by some early changes with which some familiarity is necessary. **Rigor mortis** is a stiffening of muscles due to a chemical change in which there is precipitation of protein. It begins first in involuntary muscles, affects voluntary muscles in about ten hours, and passes off in three or four days. The time of appearance and degree of rigor mortis are affected by a number of conditions, so it is unreliable as an indicator of the exact time of death. **Livor mortis** is the

reddish discoloration of dependent portions of the body, due to the gravitational sinking of blood. Internal organs, such as the lungs, are affected as well as the skin. Hemolysis of red cells occurs with varying rapidity after death, and hemoglobin may lightly stain the aortic lining or serous surfaces. Hemoglobin staining may be hastened in death from infections, particularly if due to hemolytic organisms.

Putrefaction in the dead body follows entrance of saprophytes, usually from the intestinal tract. It results in production of gases, and a greenish discoloration of tissues. Gas-producing saprophytes may cause a foamy or spongy appearance of organs, particularly liver.

Autolysis is the self-digestion or breakdown of tissues due to ferments produced in the body after death. In some tissues, such as the mucosa of the stomach or gall bladder, autolytic changes are rapid, and good microscopic preparations of such tissues may be difficult to obtain post mortem. In general, the highly differentiated tissues, e.g., the ganglion cells in the nervous system and glandular epithelium, undergo more rapid autolysis than do supporting or connective tissue structures. Early autolysis results in loss of cellular detail in staining and may cause some confusion in differentiation from such degenerative processes as cloudy swelling.

PIGMENTATIONS

In a number of conditions colored materials are deposited in the skin or internal tissues. Though considered here together, they have nothing in common except the pigment deposition. There are two classes of pigmentations: (1) Endogenous pigmentations, in which the colored substance is produced within the body, and (2) exogenous pigmentations, in which the pigment is introduced into the body by way of the intestinal tract, skin, or lungs.

Endogenous Pigmentations

There are three types of pigments produced in the body, melanins, hemoglobin derivatives, and lipochromes.

Melanin.—Melanin forms the normal coloring matter of the skin and choroid coat of the eye. It is produced in the skin by melanoblasts, situated in the basal layers of the epidermis. These specialized cells may be distinguished, even though they contain no pigment at the time, by the dopa reaction (see p. 635). Pigment-carrying cells are present in the subepithelial tissues. The amount of melanin in

the skin is increased by exposure to sunlight. Skin pigmentation is increased in Addison's disease (see p. 547), and pigmented spots are common in association with multiple neurofibromatosis. Patchy areas lacking pigment also occur, and there may be a congenital absence of melanin pigment (albinism). Benign pigmented nevi and malignant melanomas are tumors composed of melanoblasts. The amount of pigment found in such tumors shows extreme variation. Melanomas commonly arise from the skin or eye. They occur less frequently in the Negro race, and trauma is frequently an important factor in initiating a malignant change.



Fig. 5.—Malignant melanoma of the eye. The highly pigmented tumor tissue almost fills the chambers of the eye and is spreading on the outer surface. (From Surgery 9: 425, 1941.)

Ochronosis is a rare type of pigmentation by a melanin, in which cartilage is affected. Discoloration of the cartilage of the ear and nose may be visible through the skin. Most cases are due to a congenital metabolic disturbance evidenced by alkaptonuria. Some cases are due to phenol absorbed from surgical dressings.

Melanosis coli is a black discoloration of the mucosa of the large intestine. The pigment is not a true melanin (see p. 501).

Hemoglobin-Derived Pigments.—Hemoglobin, the pigment of red blood cells, is a combination of a pigment complex, *heme* + a protein, *globin*. Three types of pigments may be

formed from hemoglobin breakdown: hemosiderin, bilirubin (hematoidin), and hematin.

HEMOSIDERIN.—Hemosiderin is a brownish granular pigment formed when hemoglobin breaks down in tissues (e.g., as the result of hemorrhage). Hemosiderin is formed within phagocytic cells of the reticulo-endothelial system, and the time for its production may be as short as one day. Hemosiderin has no exact chemical composition but contains loosely bound iron which gives a Prussian blue reaction (a blue color with potassium ferrocyanide and hydrochloric acid). The iron is present mainly in the ferric form.

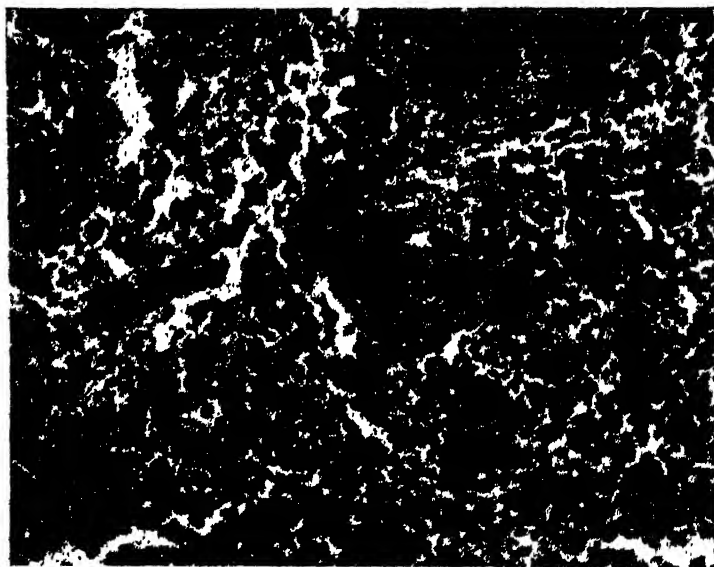


Fig. 6.—Hemosiderin pigment in spleen.

The normal continuous breakdown of red blood cells in the reticulo-endothelial system results in some hemosiderin deposition in the liver and spleen. Pathologic excess of hemosiderin deposit occurs in these organs and elsewhere whenever there is excessive breakdown of blood. Such occurs in local areas of hemorrhage, in hemolytic anemias (e.g., pernicious anemia, sickle-cell anemia), and in passive congestion of organs, where stagnation in capillaries results in

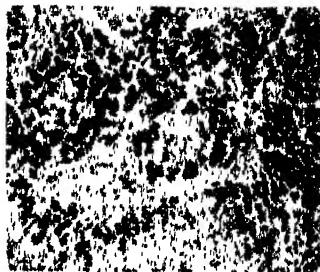


Plate III.—Hemochromatosis: 1. Liver and spleen, showing brownish pigmentation and fibrosis. 2. Liver, showing area with development of carcinoma. 3. Section of liver, showing hemosiderin deposition and fibrosis. 4. Liver, Prussian blue stain, showing iron content of pigment. 5. Pancreas, showing pigmentation and fibrosis. 6. Thyroid, Prussian blue stain, showing hemosiderin pigmentation.

increased blood destruction. In the spleen, hemosiderin pigment is found in phagocytic cells of the pulp and sinuses. In the liver, the pigment is found both in the phagocytic Kupffer cells of the sinusoids, and in the liver cells. In the kidney, tubular lining cells, as well as interstitial tissue and endothelial cells, may contain pigment. In the lung, hemosiderin pigment is often abundant in large mononuclear phagocytic cells in alveoli, when there is chronic congestion. These pigmented alveolar macrophages are often called "heart failure cells" because of their association with circulatory failure.

Hemochromatosis is a rare disturbance of iron pigment metabolism, usually occurring in males past middle life. It is characterized by excessive hemosiderin pigmentation of the skin and viscera, particularly liver and pancreas, with associated fibrosis of involved viscera. In some cases the pancreatic fibrosis is sufficient to cause functional disturbance and diabetes is present. Such cases have been labelled "bronzed diabetes." While the pigment is predominantly hemosiderin, some yellowish pigment, hemofuscin, may be present as well. Fibrosis in the liver is primarily about portal areas, but later becomes widespread and associated with atrophy of liver cells. Pancreas, spleen, and lymph nodes similarly become pigmented and fibrosed. Affected organs have a deep brown color. The total amount of iron in the body, normally about 3 grams, may be increased as much as twelve times. The disturbance seems to be an in-born error of metabolism rather than due to increased blood destruction.⁹

BILIRUBIN AND HEMATODIN.—Bile pigment is formed from the breakdown of hemoglobin by reticulo-endothelial cells, particularly in the spleen, liver, and bone marrow. Excessive bilirubin in the circulation causes the yellowish pigmentation known as jaundice or icterus.

Hematoidin is a pigment, closely related to or identical with bilirubin and formed in tissues from hemoglobin. Like hemosiderin, its formation is intracellular, but several days are required to produce hematoidin. It is formed mainly in tissues wherein a good oxygen supply is lacking. Hence it is often found where there is breakdown of blood in dead or dying tissues, as in infarcts. Hematoidin may be seen as amorphous yellow granules, or sheaves of crystals. It does

not give the Prussian blue reaction for free iron, but does give the Gmelin reaction for bile.

HEMATOPORPHYRIN is a pigment normally found in minute amounts in the urine. In a rare inborn metabolic disturbance, congenital hematoporphyrinuria, large amounts of porphyrins are found in the urine, which is colored Burgundy red. Individuals having this disease are abnormally sensitive to light.¹⁰

HEMATIN AND MALARIAL PIGMENT.—Hematin, which may be formed by the action of acids or alkalis on hemoglobin, is not a normal breakdown product of hemoglobin, nor a precursor of hemosiderin and bile pigments. However, Fairley¹¹ has indicated the possibility of its formation in some cases of intravascular hemolysis or hemoglobinemia. In such cases it rapidly combines with blood proteins to form methemalbumin. In the tissues, hematin appears as a brownish granular pigment resembling hemosiderin. However, its iron is firmly bound, so that it fails to give a Prussian blue reaction as does hemosiderin.

In massive hemoglobinurias such as may result from transfusion reactions, casts of hematin pigment may be formed in renal tubules by the action of an acid urine and are a contributing factor in the resulting renal failure.

Malarial pigment is a closely related (hematin) compound formed by action of the malarial parasite on the hemoglobin in the red blood cell.¹² Massive deposits of this brown pigment which fails to stain for iron are formed in reticulo-endothelial cells of spleen and liver (see p. 166).

Lipochrome Pigments.—Lipoid pigments are found in small amounts in various places in the body. Some of these are probably related to carotene, a vegetable pigment ingested with food. The yellowish pigment of the corpus luteum is a lipochrome. Certain lipochromes are said to be the result of wear and tear of tissues. Brown atrophy of the heart is a senile condition in which lipochrome pigments are visible at the nuclear poles of heart muscle fibers. The heart has a brownish discoloration and is small due to atrophy of the muscle fibers.

Exogenous Pigmentations

Colored materials may gain entrance to the body by inspiration, ingestion, and inoculation into the skin. Pigmentation of the lung by inspired substances such as carbon forms an important group of pulmonary conditions known as the pneumoconioses (see p. 369).

Silver poisoning or *argyria* may cause a permanent pigmentation of the skin. Excessive administration of a silver compound over a long period of time results in deposition of pigment in the upper layers of the corium, immediately under the epithelium and around sweat and sebaceous glands. The skin acquires an unpleasant, permanent, ashen-gray hue. In severe cases, pigment is present in the kidney and liver as well. The pigment, an insoluble albuminate of silver, appears to be deposited in the cement substance between cells.

Lead poisoning (plumbism) may cause pigmentation of oral mucosa. A line of deep blue pigmentation develops at the junction of teeth and gums, due to the formation of lead sulfide.

Carotenemia is a pale yellowish discoloration of the skin due to excessive ingestion of plant pigments, such as the carotene found in carrots. No deleterious effects are known.

Tattoos are pigments introduced into the skin by a needle or other sharp instrument for decorative purposes. The pigment may be seen as small granules held in the corium by macrophages. Infections, such as syphilis, may be introduced at the time of tattooing by unclean habits of the operator.¹³

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CHAPTER III

DISTURBANCES OF CIRCULATION

The proper distribution of blood and fluid to and from tissues by the cardiovascular and lymphatic system is a requisite for health. Disturbances in this function are due to a variety of causes, are of various types, and are essential parts of many diseases. Details of many of these are considered in discussion of the various organs, but the general principles are considered together here.

Congestion (hyperemia) is an excessive supply of blood and may be local or generalized. The opposite condition; **ischemia**, is a localized anemia due to interference with the blood supply to the area. It is often due to changes in the blood vessel wall (e.g., arteriosclerosis) or to intravascular clotting of blood (**thrombosis**). The portion of a thrombus or other solid, semisolid, or gaseous material carried in the blood stream and occluding vessels in another region is called an **embolus**. Necrosis of tissue resulting from blockage of blood supply by an embolus or thrombus is **infarction**. Hemorrhage is the escape of blood from vascular channels and may be due to rupture of a vessel or abnormal permeability of vessel walls. **Edema** is an excess of fluid in tissue spaces. **Lymphedema** is that type due to blockage of lymphatics.

CONGESTION

The amount of blood in a part is not constant but can be varied tremendously by dilatation of blood vessels in the tissue. In most resting tissues only a small proportion of capillaries are dilated and actively carrying blood at one time. Congestion of a tissue may be due to an active dilatation of blood vessels (**active hyperemia**) so that more blood is brought to and flows through the area. Such an active hyperemia develops in an exercised muscle, and also in acute inflammation. **Passive congestion** occurs when the increased amount of blood in the tissue is due to interference with its outflow (i.e., venous obstruction), so that the blood tends to accumulate in the tissue. Such passive congestion is localized when there is local interference with venous return (e.g., due to venous thrombosis), and generalized when the whole venous return to the heart is insufficient. This latter

condition is the characteristic of cardiac failure. The generalized chronic passive congestion of cardiac failure is commonly associated with dyspnea, cyanosis, and edema.

In certain organs, chronic congestion produces characteristic changes. The liver is enlarged and the cut surface has a characteristic mottled appearance resembling the cut surface of a nutmeg (nutmeg liver). The mottling is due to redness of the central part of the liver lobules around the central veins, contrasted with grayish peripheral portions of the lobules. Due to the anoxia of continued severe congestion, the liver cells around central veins undergo fatty degeneration, or atrophy and disappear. In long-standing cases the loss of liver cells and relative increase of connective tissue produces shrinkage and cirrhosis of the liver (cardiac cirrhosis).

The congested spleen is enlarged, has a tense capsule and a dark-red, firm, cut surface. Excessive blood content is evident in the splenic pulp.

Chronic passive congestion of the lung results in some edema, and passage of red cells from the distended capillaries into alveolar spaces. Here the hemoglobin breaks down, and the hemosiderin produced is ingested by macrophages. Because of their frequent association with the congestion of cardiac failure, such hemosiderin-laden phagocytes in alveolar spaces are called "heart failure cells." In long-standing cases, the hemosiderin may be sufficient to give the lung a brownish tinge, and increased firmness of lung tissue results from connective tissue increase in alveolar walls. Such a result is called "brown induration" of the lung (see p. 364).

ISCHEMIA

Ischemia is a decrease of blood flow to tissues, due to contraction or constriction of vessels. This may be due to (1) spasm of small arteries (ergot poisoning, Raynaud's disease), (2) disease of the arterial wall itself with narrowing of the lumen (arteriosclerosis, thromboangiitis obliterans), (3) external pressure on a vessel (tumors, amyloid deposits, etc.), and (4) blockage of the lumen by a clot (thrombosis, embolism). Gradual decrease of blood supply to a tissue brings about atrophy and disappearance of parenchymal cells. Sudden ischemia causes necrosis (infarction or gangrene), unless a collateral circulation can supply sufficient blood.

Clotting of Blood.—When blood escapes from its containing vessels, it rapidly undergoes coagulation. This is a valuable protective measure which tends to prevent excessive blood loss. In certain conditions this mechanism is defective (e.g., hemophilia), and the time consumed in clotting is excessive, or coagulation may entirely fail. Such conditions are considered in Chap. XVII. The mechanism of coagulation is complicated and not entirely understood. Injured platelets or tissue juices release a substance, thromboplastin (cephalin), which with prothrombin, and activated by calcium salts, becomes thrombin, and in turn converts the fibrinogen of the plasma into fibrin. The fibrin threads enmesh blood elements and form a clot. The action may be expressed as the following two-stage process:

1. prothrombin + calcium + thromboplastin = thrombin

2. thrombin + fibrinogen = fibrin (clot)

The essential role of vitamin K in the formation of prothrombin is a recent important discovery.

Thrombosis.—Thrombosis is the coagulation of blood within vessels during life. Due to its formation in a moving stream of blood, the structure of a thrombus differs from that of an extravascular clot. A post-mortem intravascular clot also differs in structure from an extravascular clot, in this instance due to the length of the clotting period in the former, which allows time for settling out of blood elements and production of a layered clot.

Important factors favoring thrombosis are (1) slowing or eddying of the blood stream, (2) injury to the lining of a blood vessel, or (3) alterations (physical and chemical) in constituents of the blood. The importance of slowing of the blood stream is indicated by the frequency of thrombosis in veins, particularly where there is stasis, as in the varicose veins of hemorrhoids. Eddying of the blood stream is one of the factors which promote thrombus formation in an aortic aneurysm. Injury to lining endothelium is perhaps the most important single factor causing thrombosis. It is operative in arteriosclerotic changes which often are associated with thrombosis (e.g., in coronary thrombosis) and in inflammatory and infective lesions of vessel walls and heart valves (endocarditis).

Thrombosis is very common, being found in 6 to 24 per cent of autopsies. It is much more frequent in middle age and beyond than in young individuals. Thrombosis in deep veins of the leg has been found in more than 50 per cent of persons past middle age.^{3, 4} It is particularly likely to oc-

cur in association with congestive cardiac failure, i.e., with chronic passive venous congestion. Thrombosis in pelvic and leg veins is also a common complication following surgical procedures.

The structure of a thrombus has distinctive features, due mainly to its formation in a moving stream of blood. Platelets adhere to vascular endothelium at the site of thrombus formation, which is often some point of endothelial injury. The platelets form ridges which are at a right angle to the direction of the stream. The platelets become welded together in masses and their individual outlines are lost. Filaments of fibrin form around them, which quickly enmesh passing red cells and leucocytes. The result is a laminated clot, which may be red, grayish-red, or gray, depending on the relative proportions of red cells and platelets. On the surface of the thrombus grayish irregular lamellae of platelets can be seen, the so-called "lines of Zahn."

Once the thrombus has occluded a vessel, growth is by accretion in a stagnant stream, so that an ordinary homogeneous red clot is formed. By this means a thrombus acquires a "head" and "tail." Thrombi tend to be dry, friable, adherent to the vessel wall at some point, and invaded by connective tissue (organized) in proportion to their age.

Post-mortem intravascular clots have a distinctive layered structure because they develop slowly in stagnant blood. There is time for gravity to separate the elements of the blood before coagulation is complete. The heavy red cells form a thick layer at the bottom, above which is a grayish layer of leucocytes and on top a grayish-yellow layer of plasma containing platelets and leucocytes. These layered clots are often found in the heart at autopsy. The deep red portion (crur clot) is in the dependent part, while the upper part is a tough, elastic, yellowish, translucent mass resembling chicken fat ("chicken-fat clot"). These features plus the absence of adhesion to the endothelial lining usually enable distinction from an ante-mortem thrombus.

The fate of a thrombus may be (1) degeneration and absorption, (2) calcification (phlebolith formation), (3) organization, often with recanalization of the vascular lumen, (4) embolism or spread in the blood stream to a new situation.

Embolism.—An embolus is some solid or other foreign material carried in the circulation to a point different from its origin, where it blocks the lumen of a vessel. Emboli may be composed of portions of a thrombus, tumor cells,

fat, air, masses of bacteria, or masses of parasites (e.g., malarial parasites). Emboli are carried until a vessel is reached with a caliber small enough to block further progress of the mass. Hence emboli originating in the right side of the heart or in the venous system usually become arrested in the lungs (except those originating in the portal system, which go to the liver). If the origin is from the left side of the heart or from the arterial system, arrest of the embolus is in some more peripheral part of the arterial system.



Fig. 7.—Organized and recanalized arterial thrombus. The wavy dark line is the internal elastic lamina.

Embolism of tumor cells is one of the chief methods by which malignant tumors spread, with the formation of new or metastatic tumors in distant organs. Vein walls are more

easily penetrated by invading tumor cells than are arteries. Hence tumor embolism is mainly venous, and spread is most frequently to liver and lungs.

Fat embolism may follow injury to bones containing fatty marrow (e.g., fractures), or injury to adipose tissue. The contents of injured fat cells are sucked into ruptured veins. The fat becomes lodged in pulmonary capillaries, though some may pass through these capillaries to lodge in other tissues, such as the brain.^{5, 6}

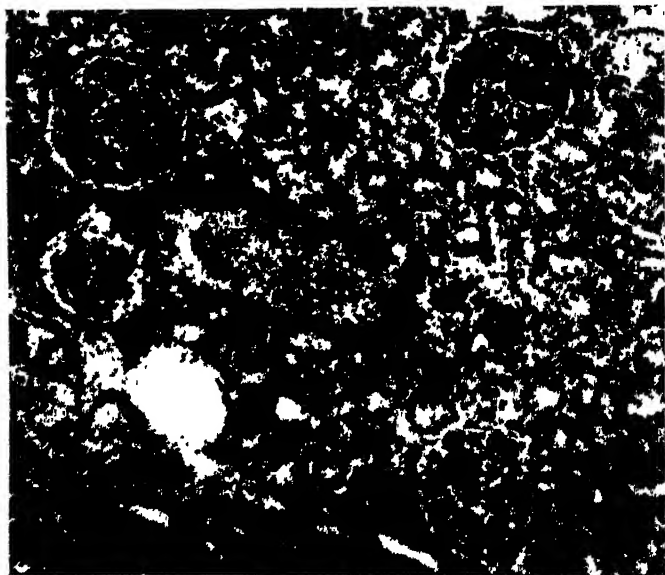


Fig. 8.—Fat embolism of kidney. The fatty material appears black.
(U. S. Army Medical Museum, courtesy Major Arthur C. Allen.)

Air embolism is a rare complication of artificial pneumothorax, and of surgical operations, particularly in the neck. It has resulted also from injection of air into a pregnant uterus in attempted abortion. In fatal cases, frothy blood is found in the vascular system, and particularly in the right side of the heart. Post-mortem demonstration is best accomplished by opening the heart under water after tying off the large vessels.

Caisson disease is a gaseous embolism which may occur in individuals working in compressed air, e.g., in construction

of tunnels, or in diving. The very high atmospheric pressure causes solution of additional air in the blood. If the pressure is then rapidly reduced, nitrogen bubbles form in the blood, and embolism results. This may cause serious disturbances in the circulation of the nervous system, lungs, and other organs.⁷ A similar type of air embolism may occur in aviators on rapid ascent to high altitudes.⁸

Embolism from a thrombus is the most common type of embolism. The effects depend on (1) whether the embolus is septic or noninfected, (2) the size of the embolus, and (3) the vessel in which it becomes arrested. Emboli arising in systemic veins ordinarily become arrested in the liver or lungs, but rarely the general systemic circulation may be reached by passing from the right to the left side of the heart through a patent foramen ovale (paradoxical embolism).⁹ Other cases of aberrant embolism appear explainable on the basis of the vertebral venous system. Pulmonary embolism is particularly important as a cause of death.¹¹

Septic embolism produces inflammation at the site of arrest. If the organisms carried in the embolus are pyogenic, abscesses are produced. Emboli arising from infected heart valves in acute endocarditis thus spread infection to other organs. Infection of vein walls often gives rise to septic embolism; e.g., infection of veins about the appendix in acute appendicitis may result in septic embolism to the liver, with multiple abscess formation in that organ (pyelephlebitis).

Infarction of tissue or gangrene may result from bland embolism, as well as from thrombosis, if the area supplied by the occluded vessel is unable to obtain sufficient blood supply through collateral vessels. Gangrene may result from arterial embolism in a large vessel of an extremity. Infarction occurs in internal organs such as the spleen, kidney, heart, lungs, intestine, and brain. Massive embolism in pulmonary or cerebral arteries may cause sudden death, without sufficient time for production of an infarct (see p. 365).

Infarction.—An infarct is an area of necrosis caused by interference with blood supply. The usual cause is rapid occlusion of an artery or vein by thrombosis or embolism. The effect produced depends on the efficiency of collateral circulation. If anastomotic supply is good, there may be but slight and temporary interference with the circulation and no infarction. If collateral circulation is insufficient to nourish the tissue, or if the obstructed vessel is the only source of supply to the tissue beyond (an end artery), death of tissue or infarction results.

Infarcts are most common in the spleen, kidneys, lungs, intestines, heart, and brain. Cardiac infarcts usually are the result of coronary thrombosis rather than embolism and are an important cause of disability and death (see p. 267).



Fig. 9.—Infarcts of the spleen. From a case of bacterial endocarditis. (Courtesy Dr. H. C. Schmeisser.)

Intestinal infarcts involve a segment or length of intestine, are associated with paralytic obstruction of the bowel, and unless surgical relief is prompt result in death from peritonitis (see p. 498).

In the lung, due to its abundant circulation, infarction follows thrombosis or embolism only when there is already some interference with circulation, such as a chronic passive congestion. The liver likewise has an abundant circulation, and in this organ infarction is rare.

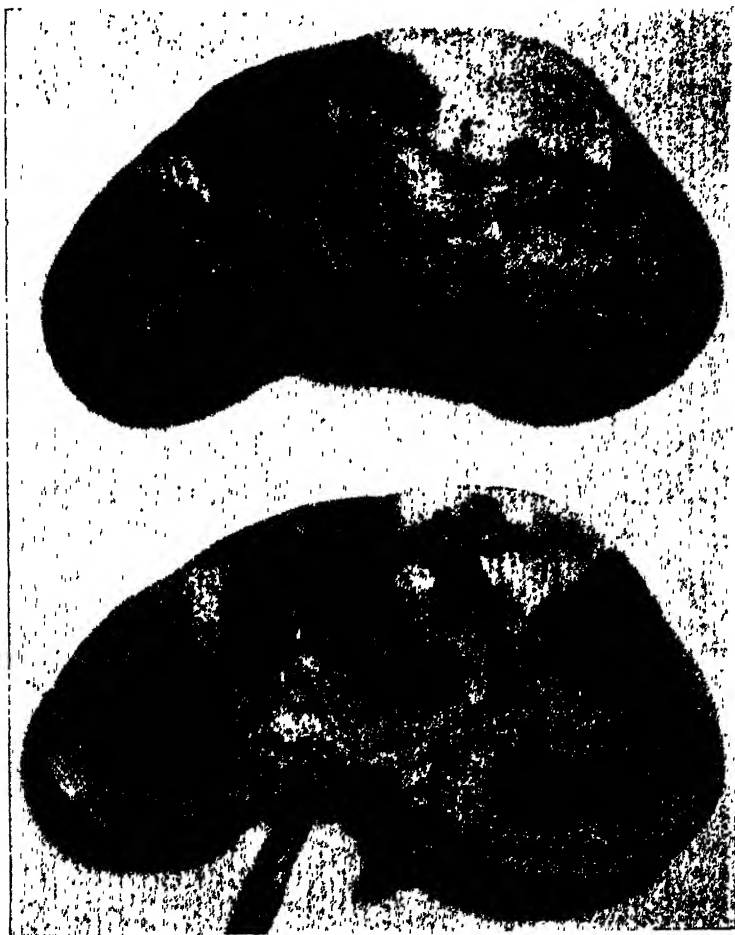


Fig. 10.—Infarcts of the kidney. The characteristic triangular shape is seen on the cut surface. (Courtesy Dr. H. C. Schmeisser.)

In the spleen, kidneys, and lungs, an infarct forms a slightly-raised pyramidal mass of dead tissue, with its base

at the periphery of the organ and its apex toward the point of arterial obstruction. Promptly after the vascular obstruction, the area becomes red and congested due to dilatation of vessels and flowing of blood into the part from adjacent vessels. Hemorrhage occurs due to injury of vessel walls and is particularly marked in infarcts of the spleen and lungs. The area becomes swollen and edematous. The amount of redness and congestion varies in different organs. In some cases it may be slight, but in some organs, such as the lung, it is always marked (red infarct). About two hours after the vascular obstruction degenerative changes appear in the cells, and within forty-eight hours necrosis is evident. Necrosis affects first the parenchymatous tissue, but eventually the less sensitive supporting connective tissue is affected as well.

The tissue around the necrotic area reacts by inflammation, so that infarcts are surrounded by a zone of hyperemia and infiltration of inflammatory cells. The necrosis is of a coagulative type, except in the brain where it is liquefactive. The infarct is gradually decolorized and forms a yellowish-white opaque area (pale or white infarct). Fibroblastic proliferation and organization proceed in the dead area, which shrinks and falls below the surface of the organ. The end result may be a shrunken and depressed fibrous scar.

EDEMA

Edema is an excessive accumulation of fluid in tissue spaces. Hydrothorax and hydropericardium refer to excess fluid in the pleural and pericardial sacs, and ascites is excess fluid in the peritoneal cavity. Anasarca is a generalized subcutaneous edema. Edematous tissue usually "pits on pressure," i.e., pressure, as by the finger, displaces fluid from the tissue and leaves a dent, which is slowly filled in as the fluid flows back into the area.

Factors governing interchange of fluid between capillaries and tissue spaces are (1) hydrostatic capillary pressure, tending to force fluid through capillary walls; (2) colloid osmotic pressure of plasma proteins which tends to hold fluid in capillaries, and to draw it from tissues into blood; and (3) the permeability of the capillary walls. The delicate normal balance may be disturbed and excess fluid pass into the tissues under the following circumstances:

1. **Increased Hydrostatic Pressure in Capillaries.**—Normally, the hydrostatic pressure in the arterial end of capil-

laries is such that the reverse force exerted by plasma proteins is overcome and fluid flows into intercellular spaces. In the venous end of capillaries the hydrostatic pressure is low and the fluid which has not been carried away by lymphatics is abstracted from tissue spaces into blood. This balance of hydrostatic pressure is upset by venous congestion. The general venous congestion of heart failure or decompensation is the most common cause. Hence cardiac failure is commonly associated with widespread edema (**cardiac edema**). Other instances of edema due to more localized venous congestion include the ascites associated with the portal congestion of cirrhosis of the liver, and edema of the ankles in pregnant women which may result from pressure of the enlarged uterus on iliac veins.

2. **Edema Due to Lowering of Plasma Proteins.**—The main plasma protein important in this regard is albumin. It acts to maintain the osmotic pressure of the blood plasma and the normal plasma volume. Globulin is relatively unimportant in this function since it exerts but one-fifth the osmotic pressure of the albumin fraction in normal serum. A level of serum albumin less than 2.5 or 3 Gm. per 100 c.c. is associated with edema. This may be due to (1) excessive loss of albumin in the urine in renal disease (**renal or nephrotic edema**), and (2) failure of sufficient formation of serum albumin due to undernourishment from famine or disease (**nutritional edema**). Experimental removal of plasma proteins by "plasmapheresis" (repeated bleeding with return of washed red cells to the circulation) reproduces this type of edema. Sodium chloride plays a secondary role in renal edema, as a sufficiency of the sodium ion in the edema fluid is a requisite for its retention by tissues. Hence salt deprivation may decrease the edema, even though salt retention by the kidney is not the primary cause.

3. **Edema Due to Increased Capillary Permeability.**—Capillary walls are normally freely permeable to water, crystalloids, and dissolved gases, but nearly impermeable to proteins. In conditions of toxic damage to endothelium, and in full paralytic dilatation, capillaries become readily permeable to plasma proteins. Diffusion of proteins into the tissues lowers plasma osmotic pressure and increases tissue fluid osmotic pressure. Such occurs in acute inflammation, and in **inflammatory edema** the tissue fluid has a high protein content. A similar increased permeability due to toxic capillary damage is a factor in the edema of acute nephritis, in snakebite, and in **angioneurotic edema**.

The main factors in edema are outlined in Table II.

TABLE II

TYPE OF EDEMA	MAIN FACTOR	SECONDARY FACTORS
Nephrosis and chronic nephritis ("Renal edema")	Low serum albumin due to loss in urine	Amount of ingested salt
Nutritional edema	Low serum albumin due to defective regeneration caused by under-nourishment	
Cardiac edema	Increased hydrostatic pressure in capillaries due to venous congestion	Oxygen lack may cause increased protein permeability of capillaries
Inflammatory edema	Abnormal permeability of capillaries to protein, due to dilatation and endothelial injury	Congestion with increased hydrostatic pressure
Acute nephritic edema	Abnormal capillary permeability due to toxic injury of endothelium	Lowering of serum albumin by albuminuria. Increased hydrostatic pressure due to cardiac decompensation
Angioneurotic edema	Increased capillary permeability	

Edematous tissues are thick, soft, moist, and boggy. On being cut fluid runs out freely, since it is largely free in tissue spaces. In edema of the lung, the fluid is found in alveolar spaces.

Lymphedema.—Blockage of lymphatic drainage from an extremity produces a peculiar type of edematous enlargement (elephantiasis). Filarial infection is the main cause of lymphatic blockage in tropical countries. Lymphatic destruction by operative procedures, such as in a radical amputation of the breast, results occasionally in lymphedema of the arm. A chronic hereditary type of edema affecting extremities is known as **Milroy's disease**.

SHOCK

Shock is a peripheral circulatory deficiency, or anoxemia, due to discrepancy in the size of the vascular bed and the volume of intravascular fluid.^{12, 13} It is characterized by decreased blood volume, decreased cardiac output, increased

blood concentration, lowering of blood pressure, and hyperpotassemia. Shock tends to follow severe injuries, extensive surgical procedures with much handling of tissues, large hemorrhages, extensive burns, and acute abdominal conditions.

The theories of shock are numerous, and its exact cause and nature still are debatable. Considerable evidence indicates that substances absorbed from injured tissues affect small vessels in systemic areas. These capillaries and vessels become dilated and abnormally permeable. The resulting leakage of fluid produces edema and reduces the total volume and volume flow of the blood at the same time that it increases the volume capacity.¹⁴ Lowering of blood pressure and insufficiency of the peripheral circulation are the result.

The post-mortem changes in shock include congestion of viscera with engorgement of minute vessels, and edema of tissues. Edema and congestion in the lungs are often prominent findings.

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CHAPTER IV

BACTERIAL INFECTIONS

Staphylococcal Infection

Staphylococci are pus-producing organisms which grow in grape-like or irregular clusters, are Gram-positive, and aerobic but facultatively anaerobic. The main pathogenic types are the golden *Staphylococcus aureus* and the white *Staphylococcus albus*. In cultures a hemolysin is produced, which by laking of red cells produces a clear zone around colonies on blood agar plates. Staphylococci produce an exotoxin, which originally was believed to contain several fractions, referred to as leucocidin, hemolysin, acute killing fraction, skin necrotizing fraction, and nephrotoxin.¹ *Staphylococcus* toxin is very potent in producing local necrosis, apparently acting by localized direct injury of cells. Treatment of the toxin by formalin (producing toxoid) removes its injurious properties, though it is still active in stimulating antibody formation. Toxoid is of some value in immunization of individuals subject to staphylococcal infections.

Wherever a foothold is gained in the body, staphylococci tend to produce a localized abscess. The skin is most commonly affected, with the production of furuncles (boils) and carbuncles. Staphylococci are commonly present on healthy skin, and while mostly saprophytic, some forms are pathogenic. Predisposing factors of lowered resistance or abrasions allow them to enter tissues and produce lesions. **Furuncles** usually start about hair follicles, with production of a small localized but painful abscess. The abscess ruptures and discharges its pus on the surface, followed by healing. The inflammation may extend and burrow in the subepithelial tissues, and a number of discrete areas of necrosis form in the skin from which pus is discharged. This more extensive lesion is a **carbuncle** and is particularly dangerous on the upper lip or upper half of the face, where thrombophlebitic extension may lead to cavernous sinus and meningeal involvement.

Staphylococcal septicemia may occur by extension from any localized focus. This is an extremely dangerous condition with a mortality of about 80 per cent. It results in multiple pyemic abscesses in kidneys, heart, lungs, joints,

etc. In some of these cases the original focus may be difficult to identify because it has healed or is hidden among the multiple lesions.

Suppurative nephritis due to staphylococci occasionally results from blood stream spread without a generalized septicemia. **Staphylococcal endocarditis** is one form of acute endocarditis (see p. 258) and has large, soft vegetations. **Staphylococcal pneumonia** is rare as a primary condition, but it may occur when resistance is depressed, as by epidemic influenza.^{2, 3} It is often rapidly fatal, with an alveolar exudate of hemorrhagic and edematous character, though abscess formation occurs if life continues for more than three or four days. **Osteomyelitis** is commonly a localized staphylococcal infection in bone (see p. 653). The organisms reach the bone by the blood stream from some primary, and often inconspicuous, focus. The localization in a certain site may be determined by some particular stress or injury to the bone. **Food poisoning** is sometimes caused by growth of staphylococci in spoiled food.

Streptococcal Infection

Streptococci are Gram-positive, spherical organisms which grow in chains. They are widely distributed and very common bacteria which are associated with a diversity of lesions, including tonsillitis, otitis media, cellulitis, appendicitis, wound infections, puerperal infections, bronchopneumonia, endocarditis, erysipelas, scarlet fever, and certain abscesses. Possibly associated with streptococcal infection are glomerulonephritis and rheumatic fever.

The classification of streptococci is most commonly based on their effect on blood agar.

(1) α hemolytic streptococci (*S. viridans*) on blood agar produce a clear zone and a greenish color around the colonies, due to formation of methemoglobin and H_2O_2 . The organisms of this group are of lower virulence and produce chronic or subacute inflammatory conditions.

(2) β hemolytic streptococci (*S. pyogenes* or *S. hemolyticus*) produce a clear zone or halo due to hemolysis around their colonies on blood agar. These organisms are in general highly virulent and produce acute lesions.

(3) The γ group is inert and produces neither hemolysis nor a green color on blood agar. This group is in general nonpathogenic and includes the streptococci normally inhabiting the intestinal tract.

Lancefield and Hare further subdivided the hemolytic streptococci by precipitation reactions into four groups, of which the first group (Group A) includes most of the pathogenic forms.

Whether specific strains of streptococci are responsible for scarlet fever and erysipelas is still unsettled. The hemolytic streptococci, although pyogenic, tend to produce a diffuse and spreading type of inflammation, rather than the circumscribed abscesses so characteristic of staphylococci. In addition to their pyogenicity and invasiveness, the hemolytic streptococci may produce an erythrogenic or rash-producing exotoxin. Other demonstrable toxins include a fibrinolysin, which dissolves fibrin, a hemolysin which acts on red cells, and a leucocidin which kills leucocytes. These toxins are probably factors in the invasive power of the hemolytic streptococci.

The possible etiologic relationship of the hemolytic streptococcus to rheumatic fever is still unsettled (see p. 252). However, in infections with the hemolytic streptococcus non-suppurative lesions often appear in various organs at irregular periods after the onset of the infection. The heart, kidneys, liver, spleen, etc., may show such lesions. In the heart these lesions are usually focal accumulations of lymphocytes and plasma cells. It has been suggested that such lesions are due in part to an antigen-antibody reaction, and possibly are precursors of Aschoff bodies.⁴

Wound Infections.—Invasion of streptococci through any wound of the skin, or even a small cut or abrasion, may result in a dangerous infection. The organisms may spread rapidly in subcutaneous tissues, producing a cellulitis, with diffuse suppuration in later stages. Spread is often along lymphatics, with the formation of reddish streaks (lymphangitis). When the lymphatic glands are reached, they also become swollen and tender (lymphadenitis). The more virulent infections reach the blood stream and produce general septicemia. This may be associated with severe symptoms, chills, a high fever, and a rapidly developing hemolytic anemia. Focal pyogenic lesions are not common with streptococcal septicemia as they are in staphylococcal pyemia, though lungs, joints, or heart valves may be affected. Toxic degenerative changes (cloudy swelling and fatty degeneration) are marked in the heart, liver, and kidneys, and the spleen is enlarged, soft, and of purplish-red color on the cut surface (acute splenic tumor).

Puerperal endometritis and myometritis are particularly dangerous forms of streptococcal wound infection. The raw surfaces of the post-partum uterus facilitate invasion, and rapid spread may occur by infection of lymphatics and blood vessels.

Erysipelas.—Erysipelas is a spreading streptococcal infection of the skin. The organisms enter through some minute wound or abrasion. Spread occurs by lymphatics, which are especially involved. The lesion appears as an elevated reddened area of skin with an irregular advancing margin. The inflammatory reaction in the corium is characterized by many lymphoid and mononuclear wandering cells. Suppuration is unusual unless deeper parts of the skin and subcutaneous tissues are invaded.

Scarlet Fever (Scarlatina).—Scarlet fever is caused by a strain of hemolytic streptococci in which production of an erythrogenic or rash-producing exotoxin is a prominent characteristic. The infection is usually a local one, with sore throat, accompanied by fever and a widespread skin rash. It is frequently complicated by glomerulonephritis or otitis media.

The organism produces a potent exotoxin, which by injection into the skin may be used to demonstrate susceptibility or immunity to the toxin (the Dick test). In susceptible individuals a bright red swollen area develops in about twenty-four hours. If the serum from a scarlet fever convalescent is injected into the skin of an individual suffering from the disease, the rash is blanched in that area due to local neutralization of the toxin (Schultz-Charlton phenomenon).

An inflammatory lesion of the throat is constantly present. Occasionally, invasion by the streptococci produces suppurative lesions, but most of the distant manifestations are due to toxin production. The skin rash shows marked vascular dilatation, and in late stages the lesion is infiltrated by leucocytes. A generalized lymphoid hyperplasia and some degree of acute splenic tumor are usually present. Cloudy swelling of the heart, liver, and kidneys accompanies the infection.

Acute glomerulonephritis is a complication which often develops during convalescence. It usually clears up completely but may give rise to a subacute or chronic glomerulonephritis and progress to a fatal ending. The result depends on the severity of the injury to glomeruli. The damage is believed to be caused not by the streptococci themselves but by their toxins, and the lesion may be a manifestation of an allergic reaction.

Streptococcal Sore Throat.—The hemolytic streptococcus is a common cause of sore throat, which sometimes occurs in epidemic form. Direct spread from one individual to another is common, but milk-borne epidemics also have occurred.

Streptococcal Bronchopneumonia.—The streptococcus is particularly important as a cause of bronchopneumonia complicating other infections, such as epidemic influenza (see p. 359).

Streptococcal Endocarditis.—The hemolytic streptococcus is one of the organisms which may cause acute ulcerative valvular endocarditis. *Streptococcus viridans* is the common cause of the more prolonged but equally fatal subacute bacterial endocarditis (see p. 256).

Pneumococcal Infection

The principal disease caused by the pneumococcus is lobar pneumonia (see p. 353), but less commonly it is the etiologic agent in peritonitis (in children), endocarditis, and meningitis.

Gonococcal Infection

The gonococcus, described by Neisser in 1879, is a Gram-negative pyogenic organism, characteristically seen in diplococcal form within the cytoplasm of pus cells. Gonorrhea is a disease of venereal nature, the primary acute infection involving the urethra in the male and the urethra, cervix, and Bartholin's glands in the female. In the acute stage the inflammation is characterized by congestion, swelling, and a profuse purulent exudate.

While in many cases the condition rapidly subsides and may completely clear up, there is often spread or development of chronicity. In the male, spread occurs to the posterior urethra, with involvement of prostate, seminal vesicles, and epididymis. Spread by the blood stream may lead to joint involvement (arthritis). Healing may cause damage by fibrosis, which in a joint causes decreased mobility. Fibrosis in the epididymis may result in sterility and in the urethra produces stricture and interference with urination. In the female, spread from the cervix results in salpingitis following a transient and mild endometritis (see p. 579).

Gonococcal endocarditis may result from blood stream spread of the organism. It is an acute destructive valvular involvement, with very large and friable vegetations. The valves of the right side of the heart are more frequently involved than in other types of endocarditis.

Gonococcal infection in infancy particularly involves the conjunctiva and vagina. In newborn infants an acute conjunctivitis may arise from organisms acquired in passage through the birth canal. It produces severe injury of the cornea and blindness, but its occurrence is prevented in most cases by a routine prophylactic instillation of silver solution into the infant's conjunctival sac.

Vulvovaginitis due to the gonococcus is fairly common in female infants, whereas the more cornified adult vaginal mucosa resists the infection. It is usually due to contact with materials contaminated by gonorrheal pus. The infection is usually mild and complications are uncommon. Changing the character and reactions of the vaginal mucosa by hormonal (estrogen) injections will often cure the infection.

Diphtheria

Diphtheria is a disease in which the organism forms a characteristic local lesion on the mucosa of the throat or upper respiratory passages. Widespread effects are produced by formation of a powerful exotoxin rather than by invasion or blood stream spread. *C. diphtheriae* may be identified in cultures by swabs obtained from involved mucosa spread on Loeffler's medium. Diphtheria is most common in children between 2 and 10 years of age, which is the period of greatest susceptibility. Immunity to diphtheria depends upon immunity to the toxin due to the possession of a requisite amount of antitoxin. In the Schick test to determine immunity, a minute amount of toxin is injected intracutaneously. If antitoxin (immunity) is present, no reaction occurs. A positive local reaction of congestion and inflammation, reaching a peak in about four days, indicates lack of immunity. Evanescent passive immunity is produced by injection of antitoxin contained in the serum from immunized horses. More lasting (active) immunity results from injection of modified toxin or toxoid.

The local lesion of diphtheria on the mucosa of the throat, larynx, trachea, or elsewhere is characterized by formation of a false membrane. This is composed of necrotic surface tissue welded together by fibrin and infiltrated by leucocytes. The term diphtheritic membrane frequently is used for such a pseudomembranous layer on a mucosal surface, whether it is caused by *C. diphtheriae*, by other bacteria, or by injurious chemicals such as strong acids, alkalies, or heavy metal salts.

In the pharynx the diphtheritic membrane is closely adherent, but in the trachea and bronchi the membrane is more easily detached and often coughed up in large fragments. The chief danger of the membrane is obstruction of respira-

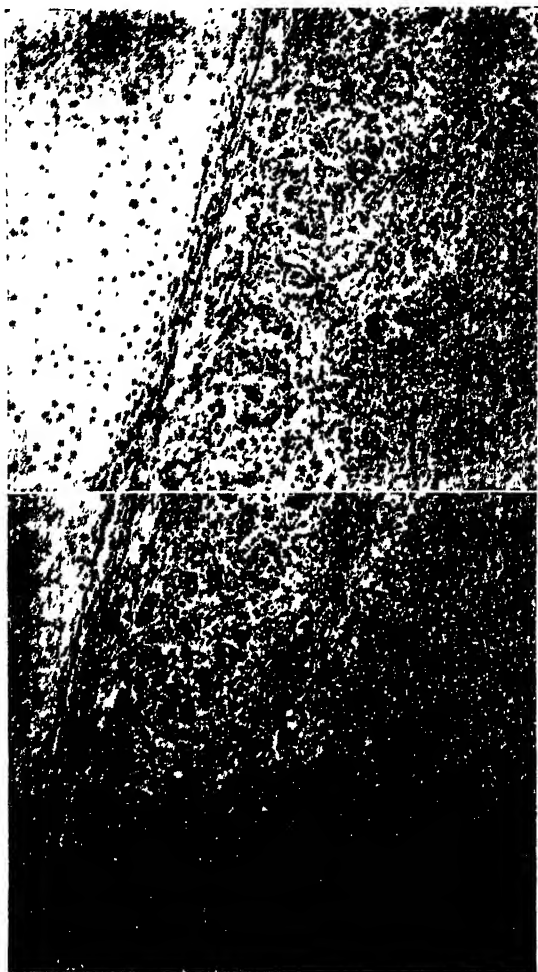


Fig. 11.—Diphtheritic tracheitis. Note the tracheal cartilage on the left, the edema and inflammatory infiltration of the tracheal wall, and the diphtheritic membrane on the right, with its abundant fibrin and inflammatory cells.

tory passages, and asphyxiation is one of the major causes of death in diphtheria. The mechanical obstruction due to the membrane is enhanced by local inflammatory swelling and edema, and by laryngeal spasm. Occasionally the diphtheria organism attacks other mucous membranes, such as of the nose, conjunctiva, or vagina.

The more distant effects of diphtheria are also serious, and mortality is frequently due to circulatory failure. This is contributed to by relaxation of blood vessels from loss of vasomotor control as well as by toxic degenerative changes in the myocardium. Bronchopneumonia, due to streptococci or other organisms, is a common complication. Degenerative changes occur in the liver, adrenals, and kidneys. In some cases the kidneys show, in addition, an acute interstitial nephritis (see p. 296). Nerve paralyses are common and are due to degenerative changes in nerve fibers. The muscles of the palate and of the eyes are most frequently paralyzed.

Tetanus

In tetanus, as in diphtheria, there is production of a powerful exotoxin with distant and far-reaching effects, although growth of the bacteria remains localized, with little or no invasion. The organism, *Cl. tetani*, is an anaerobic rod, Gram-positive, and forming characteristic terminal spores. The spores are very resistant and are common in dust and soil which has been contaminated by excreta. Infection occurs particularly in deep penetrating wounds soiled by such dirt, and in which growth is promoted by anaerobic conditions and by the presence of injured or dead tissues. The incubation period varies from three or four days up to several months. The more severe and serious cases have shorter incubation periods.

The tetanus toxin has a direct effect upon the central nervous system. Whether carried there by blood stream or by nerve fibers is a matter of debate. Hyperexcitability of the nervous system results and gives rise to muscular spasms and convulsions. The spasms often begin in the masseter muscles, and hence the term "lockjaw." No specific anatomical changes are recognizable in the nervous system or elsewhere by ordinary methods of examination.

Anthrax

Anthrax is a septicemic bacterial infection due to a large, square-ended, Gram-positive, encapsulated bacillus, which readily forms highly resistant spores. The disease is en-

zootic in certain regions among sheep, cattle, and other herbivorous animals. Human infection is mainly among individuals who handle the hides or hair of infected animals, and hence the disease is most common among tanners, butchers, brush- and hairworkers, and woolsorters. The danger of infected mink fur has been pointed out by Pinkerton.⁶ Infection is by way of the gastrointestinal tract in animals, but in man this is uncommon.

Anthrax in man is commonly an infection of the skin ("malignant pustule") or of the lungs ("woolsorters' disease"). The essential features of anthrax lesions are acute congestion, hemorrhages, and effusions of bloodstained serous fluid.

Malignant pustule is the common form of anthrax in man. The organism enters through a small abrasion of the hand, face, or neck, and in five or six days a reddened vesicle appears. This vesicle contains serous or hemorrhagic fluid and many organisms but is not purulent (and hence is not truly a "pustule"). The vesicle breaks down and forms a depressed blackened scab, surrounded by pinkish vesicles and a broad zone of edema. The lesion is often relatively painless, apparently due to axonal degeneration of local nerve fibers of the skin. The exudate in the lesion is mainly hemorrhagic, and the few leucocytes present appear unable to phagocytose the encapsulated organisms. Spread does not occur to underlying muscle.⁷ Healing and recovery may occur, or in severe cases with blood stream invasion, there is septicemia, with rapid collapse and death.

In occasional cases the primary local lesion is in the nasal mucosa, from which perineural lymphatic spread to the brain may result in a peculiarly hemorrhagic meningitis.

Woolsorters' disease occurs among workers in woolsorting and brushmaking. The infection enters by the respiratory tract. A localized lesion forms in a bronchus, from which spread produces a hemorrhagic bronchopneumonia.

In fatal cases of anthrax the blood vessels are sometimes filled with the large bacilli, a finding often prominent on low-power examination.

Gas Gangrene

Gas gangrene is an infection by one or more pathogenic anaerobes of the saccharolytic group of the genus *Clostridia* (*Cl. welchii*, *Cl. septicum*, *Cl. oedematiens*). These organisms being anaerobic, they thrive best in dead tissue and where oxygen tension is low. Hence this infection is particularly

apt to complicate wounds in which there are destruction of tissues, absence of free drainage, and some interference with circulation. The condition develops in a few hours up to a few days after infection of the wound or dead tissue. A



Fig. 12.—Puerperal endometritis and myometritis (*Cl. Welchii*). Note the sponginess of the myometrium, caused by gas formation. (Courtesy Dr. H. C. Schmeisser.)

limb in which the circulation has been cut off may have very massive involvement. In other cases of wound infection, there is an active spreading involvement of muscle. Gas production makes the tissue crepitant, and bubbles of gas may appear when the tissue is pressed upon. Muscle particularly is involved, the dead muscle appearing brown and opaque. Later the skin and other tissues become affected, and appear yellowish, greenish, or black and putrefactive. In terminal stages there may be wide dissemination of the organisms. However, in most cases where such widespread involvement of tissues is found at autopsy, the spread has been post mortem (see post-mortem changes, p. 45). Various internal organs, such as the liver, are found to be spongy and full of gas.

Puerperal infection with *Cl. welchii* or related organisms occasionally occurs, the anaerobes gaining a foothold in the necrotic material inevitably left in the uterus following delivery of the child. The wall of the uterus becomes involved, and terminally there may be extensive spread throughout the body.

Plague

Plague is an acute, highly fatal, infectious disease caused by *Pasteurella pestis*. It is primarily a disease of rats and other rodents, and is transmitted to man by fleas. Cases have occurred in western United States, where endemic foci of sylvatic plague exist among California ground squirrels. India and China are important endemic centers of plague.

The disease has been classified into bubonic, septicemic, and pneumonic forms, according to whether the lymphatic system, blood, or lungs are involved primarily. The organisms affect lymphatic tissue and blood vessels, producing a hemorrhagic septicemia, and are abundant in blood. After a flea bite or contact with infected material, spread occurs to lymph nodes, usually without development of a lesion at the site of entry. The involved lymph nodes (buboes) are necrotic and enlarged by intense congestion and hemorrhagic edema. Septicemic spread may follow, with involvement of many tissues, including lungs (secondary pneumonic plague). There is a marked destructive effect on blood vessels, and marked congestion of all organs and extensive hemorrhagic extravasations are usual. Primary pneumonic plague spreads from person to person by droplets of infected sputum. Bronchioles and alveoli are distended by a hemorrhagic exudate contain-

ing little fibrin and many organisms. Primary septicemic plague is acquired through mucous membranes of the mouth, throat, and conjunctiva.

Undulant Fever (Brucellosis)

Undulant fever has become recognized within recent years as a frequent and widespread infectious disease. The *Brucella* organisms causing the disease are of three strains, *Br. abortus*, the bovine strain from cattle, *Br. suis*, the porcine strain from swine, and *Br. melitensis*, the caprine strain from goats. The term undulant fever refers to the intermittent febrile periods which are a common manifestation. Positive diagnosis depends largely on laboratory procedures. The mortality is low, and the lesions found post mortem have varied from slight reticulo-endothelial hyperplasia to granulomatous lesions of spleen and lymph nodes resembling tuberculosis or Hodgkin's disease. Endocarditis, meningitis, and arthritis due to *Br. abortus* have been reported.

Tularemia

Tularemia is an infectious disease caused by *P. tularensis*. It is characterized by necrosis with subacute and chronic granulomatous lesions in lymph nodes, liver, spleen, and lungs. Wild rabbits form a reservoir of the disease, and most human cases are due to the handling of infected rabbits. The condition also occurs in ground squirrels, wild rats and mice. The organisms are transferred between animals by the woodtick. While most human infections are due to handling infected carcasses, it may also be transferred by the bite of ticks and deer flies.

The clinical types of the disease are (1) ulceroglandular, in which a primary lesion forms at the site of inoculation in the skin, followed by enlargement of regional lymph nodes; (2) oculoglandular, wherein the primary involvement is in the conjunctiva and is followed by lymph node enlargement; and (3) typhoid type, in which the primary point of inoculation and the lymph node enlargement are not obvious. Most cases are of the ulceroglandular type. Specific agglutinins, useful in diagnosis, develop during the second week of the infection. The disease has a mortality of about 4 per cent. A nonfatal attack confers lasting immunity.

In tularemia, there are two effects in human tissues, (a) a necrotizing effect due to the organism, producing caseous necrosis, and (b) a tissue reaction in which monocytes and

epithelioid cells predominate. In early lesions the necrosis tends to predominate, while in old lesions the cellular reaction and fibrosis are more prominent. A polymorphonuclear leucocytic reaction is usually absent unless there is a secondary infection.

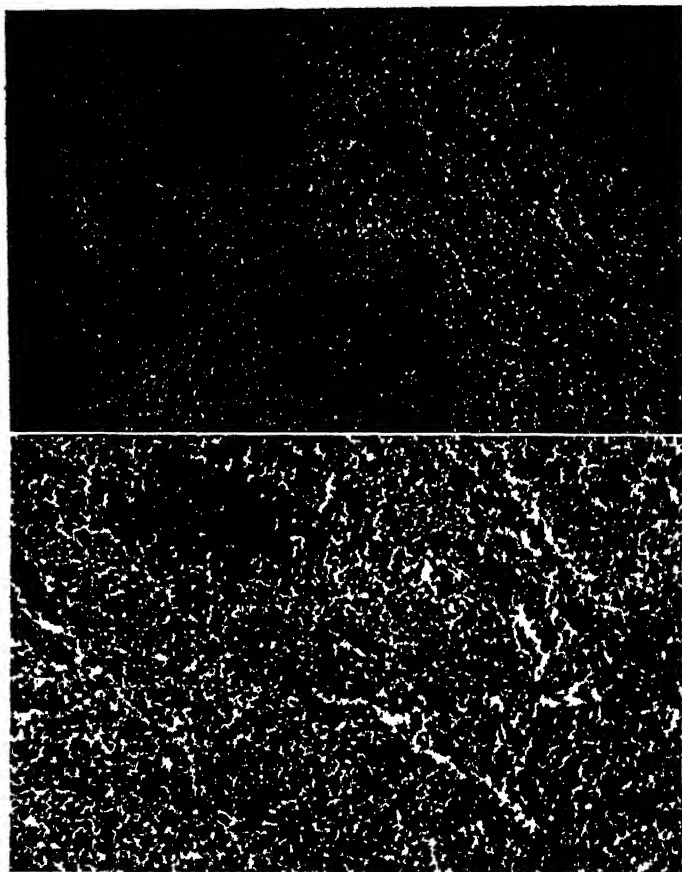


Fig. 13.—Tularemia of spleen. Note the confluent areas of caseous necrosis.

The characteristic lesions of focal caseous necrosis and mononuclear cell reaction are found in the lymph nodes draining the primary lesions, and also commonly in the spleen (70 per cent), liver (55 per cent), and lung (70 per

cent). The pulmonary involvement is a nodular or confluent pneumonia with mononuclear exudate and a tendency to caseous necrosis of exudate and alveolar walls (see p. 362). In fatal cases the necrotizing factor in tularemic lesions is particularly prominent, while in specimens from nonfatal cases the epithelioid cell reaction is more striking, and there may be multinucleated giant cells of the Langhans' type.¹³ The organisms are found in the lesions of lower animals, but are scarce and usually not demonstrable in human lesions.

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CHAPTER V

TUBERCULOSIS

Tuberculosis is a leading cause of death, although the mortality rate is steadily declining. Most of the deaths occur in infancy and early adult life. The causative organism, *Mycobacterium tuberculosis*, possesses a fatty capsule and stimulates a specific granulomatous tissue reaction characterized by caseous necrosis, pale mononuclear "epithelioid" cells, and giant cells with multiple peripheral nuclei. Human and bovine strains of the organism are important. Most pulmonary tuberculosis is caused by the human type, but the bovine type is quite commonly found in intestinal, bone, and joint tuberculosis in children. Infection with the latter type is spread by milk from infected cows and has become uncommon with more universal pasteurization. Infection with the human strain may be by inhalation directly into the lungs with droplets or dust, or through lymphoid tissue of the pharynx or intestine. The majority of individuals are infected before reaching adult life. In most cases resistance is sufficient to overcome infection with a small dose of organisms. Following this early infection there is an enhanced sensitivity or allergy to products of the organism, as manifested by a reaction to a tuberculin skin test. The lung is the organ most frequently affected, but lymph nodes, intestine, kidney, brain, meninges, spleen, and liver are also commonly involved. Spread in the body occurs by direct extension, lymphatics, blood stream and by natural passages such as bronchi.

The Tubercle Bacillus

The tubercle bacillus, discovered by Koch in 1882, belongs to the group of *Mycobacteria*. This group of "acid-fast" bacilli also includes the bacillus of leprosy and certain saprophytic organisms such as the smegma bacillus. Human and bovine strains of the tubercle bacillus commonly infect man, but human infection with the avian strain is very rare. The human strain is virulent in man and the guinea pig, but rabbits and fowls are resistant. The bovine strain, in addition to infecting cattle, is virulent for the rabbit, guinea pig, and man. The human and bovine strains, while distinguishable by cultural methods, are best differentiated by studying their relative virulence for rabbits.

The tubercle bacillus is a slender rod with a somewhat beaded or granular appearance. It can be stained in smears or tissues by the Ziehl-Neelsen method, which consists of staining by hot basic fuchsin, and decolorization by acid.

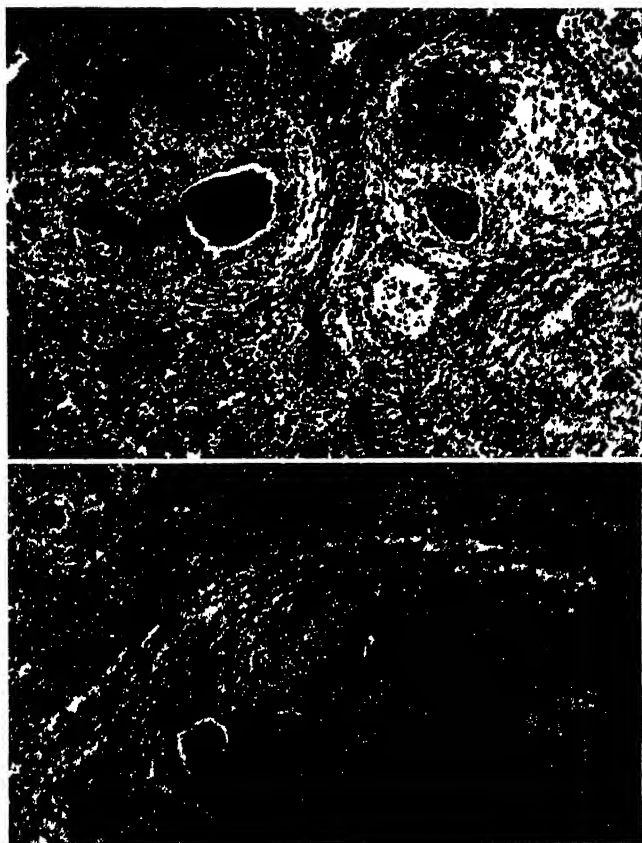


Fig. 14.—Tuberculosis of lymph node. Note the caseation, epithelioid cells, and characteristic multinucleated giant cells.

The organisms, being “acid fast,” retain the dye and are colored red. When the organisms are scanty, a concentration method, using antiformin, may be useful. When the organisms are small in number, staining methods may fail, but inoculation of infected material into guinea pigs will reveal their presence, for this animal will develop character-

istic tuberculous lesions within six weeks. Granular and nonacid-fast forms of the tubercle bacillus as well as the typical forms may be present in lesions and represent phases of growth of the organism.¹

Chemical fractions have been isolated from tubercle bacilli which on injection cause reproduction of the cellular reactions of tuberculosis, though they do not bring about any change in resistance to the disease. These chemical fractions include lipids, polysaccharides, and proteins. One of the lipids (a phosphatide) is taken up by phagocytic mononuclear cells and converts them into epithelioid cells and derivative giant cells, the characteristic cells of tuberculous lesions. Certain waxes (higher hydroxy-acids) are responsible for the acid-fastness of the bacilli, and on injection induce the formation of multinucleated giant cells of foreign body type. The polysaccharides have a chemotactic effect on neutrophils. The proteins induce a varied stimulation of monocytes into epithelioid cells, macrophages, and giant cells.²

Route of Infection

(1) Direct infection of the lung by inhalation of organisms with droplets or dust particles is the most important method of infection. (2) Infection through the alimentary tract occurs in bovine bacillus infection from milk. The organisms enter through the lymphoid tissues of the tonsils or pharynx to involve cervical lymph nodes, or through the intestine to reach mesenteric lymph nodes. No lesion may be left at the point of entry. From infected nodes, lymphatic extension to the thoracic duct and then by the blood stream may result in pulmonary tuberculosis. Except in children, the intestinal route of primary infection is probably uncommon. (3) Infection through the skin is rare, but it may occur in surgeons and pathologists who handle infected tissues. It usually results in a local lesion rather than generalized infection. (4) Congenital infection may occur when there are placental lesions, but this is rare and unimportant.

Tissue Reactions in Tuberculosis

Tubercle bacilli in tissues result in localized nodules of tissue reaction, called tubercles. The characteristic features are a core of coagulative caseous necrosis, surrounded by a cluster of peculiar mononuclear (epithelioid) cells, some of which fuse to form giant cells with multiple peripheral nuclei, and an outer border of lymphocytes.

When tubercle bacilli are injected into tissues, there is a prompt outpouring of polymorphonuclear leucocytes. Very rapidly, however, the reaction becomes mononuclear. These phagocytic cells are derived from histiocytes and rapidly engulf the organisms and degenerated leucocytes. The fatty material thus engulfed becomes dispersed in fine particles throughout the cell, giving it a distinctive appearance with resemblance to an epithelial cell. These transformed cells are called epithelioid cells. They have large oval pale nuclei, abundant pale eosin-staining cytoplasm, and are bound together by irregular branching processes. Cell boundaries are often indistinct, and the appearance is that of a syncytium. Near the central part of the cluster of epithelioid cells, there may be one or more giant cells. These are formed by fusion of epithelioid cells about a small bit of necrotic material, or possibly by amitotic division of nuclei without cellular division. They are but modified forms of foreign body giant cells. The nuclei form a ring about the periphery, or cluster at one or more poles of the giant cell.

A coagulative caseous necrosis develops in the center of the tubercle. This is caused by destructive action of bacterial products, and contributed to by the avascularity of the tubercle. No blood vessels are present within the tubercle itself. The necrotic material is granular and cheesy in its gross appearance, and usually no residual histologic evidence of tissue structure can be seen in it. Lymphocytes border the periphery of the epithelioid cluster, and as the lesion ages, fibrosis develops around the tubercle.

The several elements which compose the tubercle vary quantitatively. When dosage and virulence of the organisms are low and resistance is high, epithelioid cells are predominant, giant cells may be scarce, and there is little or no necrosis. This type of lesion is often termed a "hard tubercle." On the other hand, when the dosage and virulence are high in comparison with resistance, necrosis may predominate, and epithelioid cells are relatively scarce. These are "soft tubercles."

The smallest tubercles are of microscopic size, but their enlargement or fusion produces visible lesions. The smallest of these, about the size of a millet seed, are little grayish areas, a millimeter or two in diameter, with a minute yellowish point of necrosis in their centers.

The afore-mentioned reactions are essentially productive, but in certain situations tuberculous inflammation may be exudative. On serous surfaces such as the peritoneum, in

tuberculous pneumonia and tuberculous meningitis, there may be a serofibrinous exudate in addition to tubercle formation.

If the tubercle is very small, healing may result in its disappearance or replacement by a fibrous scar. A considerable amount of caseous material may not be absorbed, but becomes calcified by the deposition of calcium salts. This tendency to calcification is comparable to calcium deposition in any devitalized tissues in the body (dystrophic calcification) and possibly depends on a localized increased alkalinity of the necrotic material. While calcified tuberculous lesions ordinarily are considered healed, it is sometimes possible to demonstrate living tubercle bacilli in them. Under certain circumstances, the necrotic material of tubercles can be disposed of by natural passages, e.g., a tubercle in the lung may rupture into a bronchus, and the caseous mass transferred by bronchial passages leaving a cavity. The highly infective caseous material may be coughed up or inhaled into other parts of the lung.

Resistance and Allergy in Tuberculosis

Three important variable factors in tuberculosis are dosage of organisms, resistance (constitutional and acquired), and allergy. Dosage is a factor of prime importance, often determining whether the infection will be slight and easily handled, or progressive and fatal. The roles of immunity and allergy are disputed. There appear to be some differences in constitutional and racial immunity, but they are probably of less importance than environmental factors (i.e., exposure and dosage). The high rate of tuberculosis in negroes may have some basis of racial susceptibility, but environmental factors are probably of greater importance. Age appears also to be a factor in susceptibility, since children between 4 and 14 years do not often acquire tuberculosis, and individuals past middle age are affected relatively little by tuberculosis.³

Allergy, in the sense of an altered tissue reaction to bacterial products, occurs as a result of infection with tubercle bacilli. The skin reaction with tuberculin is a manifestation of this allergy. The altered form and course of tuberculosis in adults as contrasted with those of childhood tuberculosis have been ascribed to allergy resulting from childhood infection, although there is disagreement on this point.

Enhanced resistance or partial immunity to fresh infection may result from an infection which has been successfully

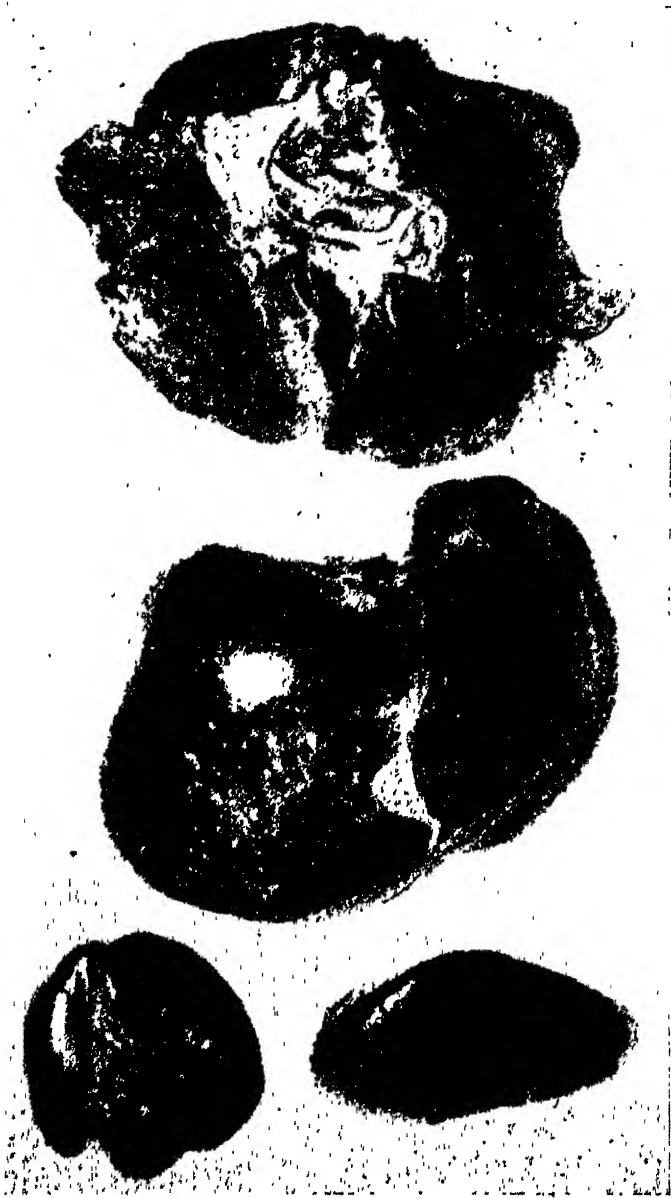


Fig. 15.—Miliary tuberculosis. Miliary tubercles in lung, liver, spleen, and kidney from an infant with acute miliary tuberculosis. (Courtesy Dr. H. C. Schmeisser.)

combated because of low virulence or dosage of organisms. While this increased resistance is usually concomitant with demonstrable allergy, there is evidence that the allergy and immunity are at least partially independent.⁵ At any rate, decisive factors determining progression of tuberculosis are dosage of tubercle bacilli and constitution, the latter including heredity, nutritional state, and resistance as modified by environment and previous infection.¹

Miliary Tuberculosis

Miliary tuberculosis is the result of widespread dissemination of large numbers of tubercle bacilli by the blood stream. Myriads of tiny miliary tubercles develop in the spleen, liver, kidneys, meninges, and other organs. The

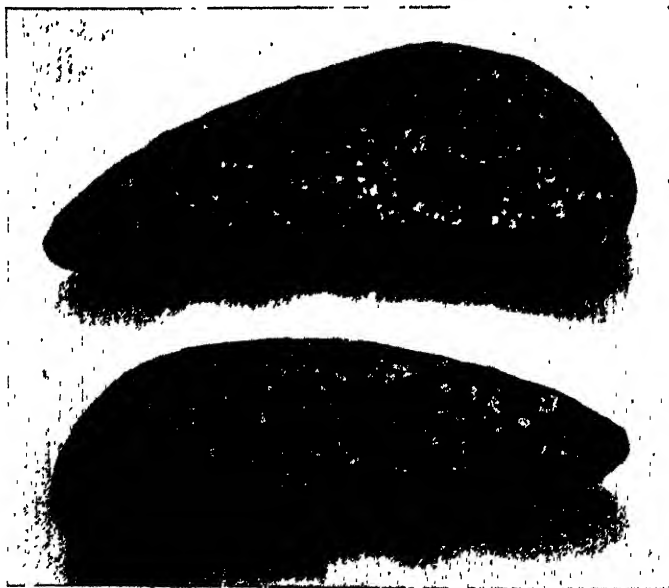


Fig. 16.—Miliary tuberculosis of spleen. (Courtesy Dr. H. C. Schmeisser.)

tubercles are seen as grayish nodules, a millimeter or two in diameter, fairly uniform in size, studding the outer and cut surfaces of affected organs. The patient exhibits fever and intense intoxication, and death usually results in a few weeks.

The spread of such large numbers of tubercle bacilli by the blood may be the result of tuberculous infection of a vessel wall with rupture of caseous material into the lumen; e.g., a tuberculous mediastinal lymph node may rupture through the

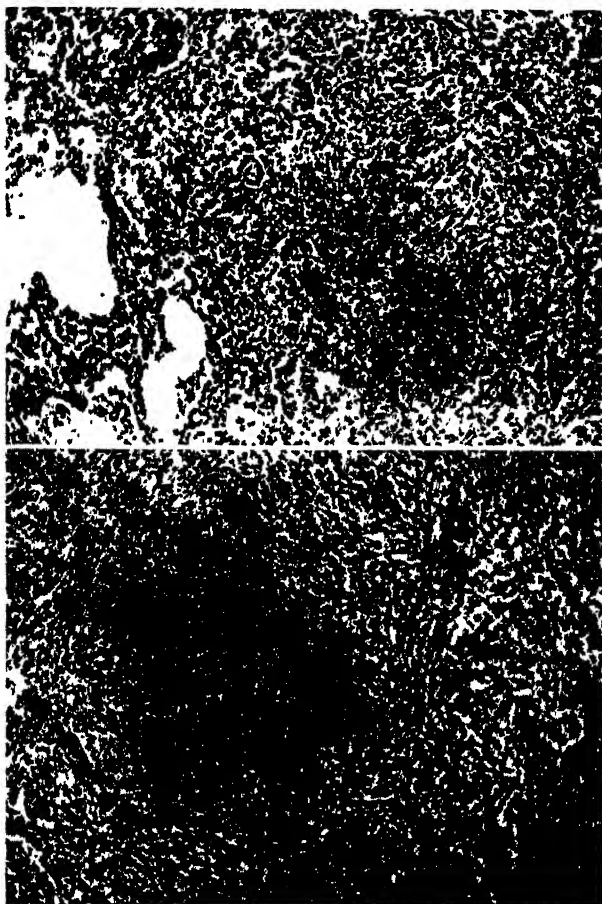


Fig. 17.—Miliary tubercles in lung. Note the focal areas of caseous necrosis, about which there is relatively little epithelioid cell formation.

infected wall of an adjacent pulmonary vein. Occasionally a lesion of the thoracic duct similarly causes massive vascular spread. Auerbach⁸ has concluded that miliary dissemination

is commonly from an extrapulmonary lesion into the draining lymphatic system, and in turn into the venous system. Usually there are multiple seedings of organisms.

Organisms spread in small numbers by the blood stream may cause a few tuberculous lesions in spleen, liver, or kidney. Many such lesions heal and are seen as rounded, grayish-white fibrous or calcified nodules, a few millimeters in diameter.

Pulmonary Tuberculosis

Childhood Type.—The childhood or primary type of pulmonary tuberculosis is characterized by development of a small peripheral or subpleural tubercle (sometimes multiple), which may develop in any portion of any lobe. It is more frequent in the lower or middle part of the lung and is rarely at the apex. This tuberculous lesion was minutely studied by Ghon and is frequently termed the **Ghon tubercle**.



Fig. 18.—Childhood tuberculosis. Large caseous masses in mediastinal lymph nodes. (Courtesy Dr. H. C. Schmeisser.)



Fig. 19.—Tuberculosis of lung, with cavitation and bronchopneumonic spread. (Courtesy Dr. H. O. Schneisser.)

It develops to a size of 1 to 3 cm., and from it spread occurs by lymphatics to mediastinal lymph nodes, which become greatly enlarged and caseous. The combination of the peripheral lung lesion and enlargement of the tracheobronchial lymph nodes is characteristic, and the two lesions together are called the **primary complex**. Progression by lymphatic or blood stream dissemination may occur, but in most cases there is healing with fibrosis or calcification. In most adult lungs healed remnants of primary tuberculous infection may be found by careful search.

Adolescents or adults not previously infected may also show the primary type of tuberculous lesion. Whether primary pulmonary infection in the adult can take other anatomic forms is still uncertain.

Most cases of bovine tuberculous infection from milk occur in childhood, but even at this age the bovine bacillus accounts for but a small proportion of tuberculosis. The infection occurs by way of the alimentary tract, with involvement of cervical or mesenteric lymph nodes. It rarely leads to pulmonary tuberculosis.

Pulmonary Tuberculosis in Adults (Phthisis).—A large proportion of individuals have had a tuberculous infection before reaching maturity, as revealed by tuberculin skin tests. This proportion varies from 30 to 90 per cent in different areas and social groups. A debated problem is whether adult tuberculosis represents a fresh infection from without, or a lighting up or reinvasion from a partially healed earlier lesion in which tubercle bacilli have remained viable.⁷ There is no doubt that both can and do occur, but it is generally considered that exogenous reinfection is the more frequent process.

In adult pulmonary tuberculosis there is a very constant localization of lesions in the upper part of the lung (apical region). The reason for this has never been adequately explained, though frequently ascribed to differences in movement of that portion of the lung.

An acute exudative tuberculous lesion develops in the subapical portion of the lung. If the infection is overcome, healing occurs with fibrosis, leaving a depressed fibrous scar at or near the apex. Such scars are very commonly found at autopsy. They usually are considered to represent such a healed tuberculosis process, but Davson has suggested that apical scars also may be due to the accumulation of inhaled siliceous dust.⁸



Fig. 20.—Pulmonary tuberculosis. Note the large cavity at the apex and the spread throughout the rest of the lung. (Courtesy Dr. H. C. Schmeisser.)



Fig. 21. Tuberculous cavity in apex of lung. White rod shows the communication of the cavity with a bronchus. (Courtesy Dr. H. C. Schmeisser.)

If the lesion progresses, a nodular mass of tuberculous granulation tissue is formed, with caseation necrosis. Healing and fibrosis about the margins result in a fibrocaseous lesion, which in some cases is well walled off and may be stationary. If healing is less complete, irregular extensions occur into the adjacent lung tissue. When a bronchial wall



Fig. 22.—Tuberculous pericarditis. Note the tremendous thickening of the pericardium, the caseation of the mediastinal lymph nodes, and the tubercles in the lungs. (Courtesy Dr. H. C. Schmeisser.)

becomes involved in such extension, the caseous material is discharged and coughed up, leaving a cavity in the lung. Such cavities may be up to 4 or 5 cm. in size, have thickened, fibrocaseous walls, and a rough irregular lining. Secondary infection by inhaled organisms is usual in these cavities.

Severe hemorrhage may occur into a cavity, but hemorrhage is usually slight or entirely lacking due to narrowing of the lumen of involved vessels by intimal thickening (endarteritis obliterans) and thrombosis. The thickened vessels are sometimes seen as firm cords traversing the cavity.



Fig. 23.—Tuberculous enteritis, terminal ileum. Note the oval ulcers which tend to encircle the bowel. (Courtesy Dr. H. C. Schmeisser.)

Spread from the active apical lesion may occur by the blood stream, giving rise to miliary tuberculosis, or by bronchial passages to other parts of the lung. With a tuber-

culous cavity in communication with a bronchus, highly infected sputum or caseous material may be aspirated into uninvolved portions of the lungs. When small numbers of organisms are so aspirated, small isolated tuberculous nodules found in the lower portions of the lung. When huge numbers are aspirated, a confluent tuberculous bronchopneumonia develops and progresses rapidly to a fatal ending (galloping consumption). With such an event, the involved portions of the lung are consolidated, airless, and have a gelatinous consistency. Microscopically, there is a massive caseation, the alveoli being filled with necrotic material. There is relatively little exudate, and few epithelioid or giant cells are formed.

Healing of tuberculous cavities of the lung is most commonly by inspissated caseous contents filling the lumen and becoming surrounded by contracted scar tissue. The bronchi entering the area become narrowed and finally have their lumens occluded. Rarely there may be healing by scar tissue with no caseous remnants remaining, or there may be "open healing," the cavity remaining open and in communication with bronchi, the fibrous wall tending to develop an epithelial lining.⁹

Extrapulmonary Tuberculosis

Tuberculous Pericarditis.—Tuberculous involvement in the pericardium is usually an extension from the lungs or mediastinal lymph nodes. It is characterized by extreme thickening of visceral and parietal layers by tuberculous granulation tissue (see p. 250).

Intestinal Tuberculosis.—Intestinal tuberculosis may be primary in infancy and childhood but is usually a complication of pulmonary tuberculosis resulting from swallowing infected sputum. It begins in lymphoid tissue of the ileum or cecum and results in ulcers whose long axes run transversely. (See p. 489.) The stomach is rarely involved.

Tuberculous Peritonitis.—Peritoneal tuberculosis may be localized around an infected mesenteric node, Fallopian tube, or other visceral lesion. A general form also occurs in which both visceral and parietal peritoneum become studded with tiny tubercles. There may be abundant peritoneal exudate (wet form), or a fibrinous exudate causing marked adhesions of viscera (dry or plastic form). (See p. 512.)

Tuberculosis of the Larynx.—The larynx often becomes infected by sputum from pulmonary lesions. Ulceration is usual, and there may be considerable destruction or fibrosis.

Tuberculosis of the Kidney.—The kidney is usually involved in generalized miliary tuberculosis. There also occurs a chronic ulcerative type of tuberculous pyonephrosis. (See p. 314.)



Fig. 24.—Tuberculous mesenteric lymph nodes. (Courtesy Dr. H. C. Schmeisser.)

Tuberculosis of the Ureter and Bladder.—Tuberculosis of the ureter and bladder is usually secondary to involvement of the kidney, and in the bladder is most prominent around ureteral openings. Cystitis often gives the first evidence of renal infection, but regresses when the infected kidney is removed.

Tuberculosis of Male Genitalia.—Male genital organs may be infected from the kidney but are most often involved by hematogenous spread. Epididymis, seminal vesicles, and prostate are often infected, but involvement of the testis is unusual.

Tuberculosis of Female Genitalia.—Of the female genitalia the Fallopian tubes are most commonly involved, and from them the infection may spread to the endometrium. (See p. 580.)

Tuberculous Meningitis.—Except when occurring as part of a miliary tuberculosis, meningeal infection is usually a spread from a caseous focus in the brain substance or choroid plexus. An abundant translucent exudate covers basal portions of the brain. In the nervous tissue itself localized tumor-like tuberculous lesions (tuberculomas) may develop to considerable size. (See p. 717.)

Tuberculosis of Bones and Joints.—Children are particularly prone to bone and joint tuberculosis, which is sometimes due to bovine infection. Spongy bone especially is attacked. Tuberculosis of the bodies of vertebrae (Pott's disease) may cause angular kyphosis. (See p. 669.)

Tuberculosis of the Skin.—There are several types of tuberculous skin lesions, of which *lupus vulgaris* is most common. *Tuberculides* are skin lesions histologically resembling tuberculosis, but in which the organisms are rarely demonstrable.

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CHAPTER VI

RICKETTSIAL AND VIRAL DISEASES

Rickettsial and viral diseases are considered together because they are closely related biologically. Both are caused by obligate intracellular parasites which lack enzymes necessary for independent metabolism, and utilize the enzyme systems of the tissue cells in which they live.

Certain bacteria may be cultivated in media containing relatively simple inorganic chemicals. Others require complex organic food substances which are found only in living animals. Rickettsiae and viruses find the metabolites which they require only within tissue cells. The nature of these metabolites is unknown, but they are believed to be intermediary products formed in the complex processes of intracellular metabolism.

Bacteria, rickettsiae, and viruses may be arranged in a series, with progressive diminution in size and progressive loss of independent metabolic activity. Bacteria and rickettsiae, with few exceptions, are unable to pass through unglazed porcelain filters. Viruses, which range from 0.250 micron to 0.008 micron in smallest diameter, invariably pass through such filters. Rickettsiae are plainly visible with the ordinary microscope, appearing within cells as minute diplobacilli. The elementary bodies of some of the larger viruses

TABLE III
RICKETTSIAL DISEASES OF MAN

	ETIOLOGIC AGENT	VECTOR	DISTRIBUTION
I Typhus Fever			
1. Epidemic	R. prowazeki prowazeki	Lice	Europe, Africa, Asia, Central and South America
2. Endemic	R. prowazeki mooseri	Rat flea	World-wide
II Spotted Fever	D. rickettsi	Ticks	World-wide
1. Boutonneuse fever	D. rickettsi conori	Ticks	Mediterranean Area
III Tsutsugamushi Disease	R. tsutsugamushi	Mites	Western Pacific Area
IV Q Fever	R. burneti (diaporica)	Ticks?	Australia, U.S.A.
V Trench Fever	R. pediculi?	Lice	Europe

are also microscopically visible, but most viruses are beyond the range of the ordinary microscope. The taxonomic separation of rickettsiae from certain of the larger viruses, such as that of psittacosis, is based on arbitrary criteria which will be considered later.

Rickettsiae and viruses, because of their complex growth requirements, cannot be cultivated on lifeless media. They may be propagated in living animals, in tissue cultures, or in the cells of the membranes of the developing chick embryo.

RICKETTSIAL DISEASES

The rickettsiae are minute organisms of bacterium-like morphology which lead an intracellular existence in the tissues of many arthropods. These organisms usually do not injure their arthropod hosts, and in several instances are transmitted from generation to generation by inclusion in the ova. Of the many rickettsiae inhabiting arthropod tissues, four are known to be pathogenic for man: (1) *Rickettsia prowazeki*, the cause of louse-borne and flea-borne typhus fever, (2) *Dermacentoroxenus rickettsi*, the cause of tick-borne diseases of the spotted fever group, (3) *Rickettsia tsutsugamushi*, the cause of mite-borne tsutsugamushi disease ("mite typhus"), and (4) *Rickettsia burneti* (*diaporica*) the cause of Q fever. *Rickettsia pediculi*, an extra-cellular organism found in the intestinal tract of the louse, is the probable cause of trench fever. The rickettsial diseases with their etiologic agents and vectors are shown in Table III. *Bartonella bacilliformis*, the cause of Carrion's disease, is not usually included with the rickettsiae, but is closely related to them, and will be discussed in this chapter for the sake of convenience.

Rickettsial diseases clinically are acute fevers, usually with characteristic skin eruptions, and variable mortality in different outbreaks. Clinically variant forms are seen, partly as a result of variation in virulence and partly because of strain modifications from prolonged residence in different arthropod and mammalian hosts. Immunologic studies have shown, however, that all rickettsial diseases known at present fall into one or another of the above groups.

The Typhus Group.—Epidemic or human typhus is numerically the most important of the rickettsial diseases. About 15,000,000 cases, with over 3,000,000 deaths occurred during and shortly after the World War of 1914-1918. In World War II devastating epidemics did not occur, a fact



Fig. 25.—Typhus rickettsiae. Photomicrograph showing a serosal cell almost completely filled with *Rickettsia prowazekii*; Giemsa-stained film preparation from the serotal sac of an infected guinea pig. (Courtesy Dr. Henry Pinkerton.)

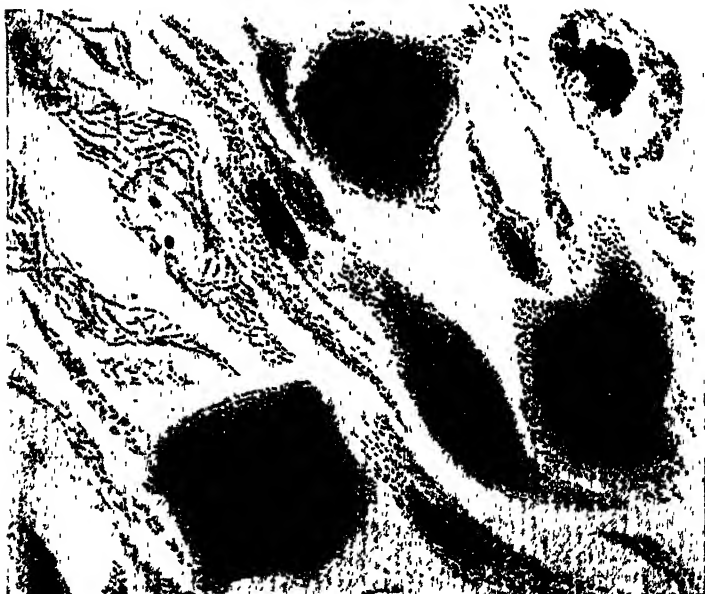


Fig. 26.—Typhus rickettsiae. *Rickettsia prowazekii* in tissue culture. Drawing showing completely and partially filled cells, one of which is in mitosis. (Courtesy Dr. Henry Pinkerton.)

which probably may be attributed largely to improved delousing methods and prophylactic vaccination. The etiologic agent, *R. prowazeki* (Figs. 25 and 26), is carried from man to man by the infected louse, *Pediculus humanus*. The organisms, which multiply in the intestinal lining cells and are present in the feces of the louse, gain entrance to dermal capillaries through the puncture wound made by the louse in feeding.

Endemic or murine typhus with a reservoir in wild rats, is transmitted to man by the bite of the rat flea. This type is clinically milder, and slight but definite immunologic differences between it and epidemic louse-borne typhus have been demonstrated. Presumably murine typhus may be transformed into epidemic typhus by repeated louse transfer, but this has not been proved.

The gross pathology of typhus is not impressive, no changes other than splenic enlargement and cloudy swelling of the organs being seen. Microscopically, there is found a generalized proliferative reaction of the endothelium of small blood vessels, often leading to thrombosis, and caused by the growth of rickettsiae in the cytoplasm of the endothelial cells. Localized perivascular collections of mononuclear cells (the so-called typhus nodules) are also characteristic. Demonstration of the organisms is difficult and requires perfect fixation and staining. Fixation in Regaud's fluid and staining by the Giemsa method are most satisfactory. Lesions are seen most strikingly in the skin, myocardium, and brain. In the myocardium, in addition to the vascular lesions, a diffuse infiltration of mononuclear cells between the muscle fibers is seen with myocardial fiber degeneration in some instances. In the brain, the characteristic focal lesions center around minute damaged capillaries. Petechial hemorrhages, perivascular cuffing, and glial nodes are also seen, so that the picture resembles that of the various types of viral encephalitis. Interstitial pneumonitis, characterized by the accumulation of mononuclear cells in the alveolar walls, often appears to be part of the picture of uncomplicated typhus fever.

Clinically, typhus is characterized by headache, mild chills, and fever which reaches its height at the end of the first week and terminates by rapid lysis, in uncomplicated cases, on the fourteenth to sixteenth days. The characteristic rash appears between the fourth and eighth days. It consists of pink macules and papules 2 to 5 mm. in diameter, which later become hemorrhagic because of thrombosis of the skin capillar-

ies. In the second week, delirium, stupor, or even coma are seen as a result of the encephalitis. Gangrene of the skin from vascular occlusion is occasionally seen. Death may be due to the myocarditis, to the encephalitis, to secondary bronchopneumonia, or to generalized toxemia. There is evidence that a shocklike condition, with peripheral circulatory failure, hemoconcentration and low blood pressure also may be important in many fatal cases.¹¹

The mortality is 20 to 70 per cent in epidemic typhus and 2 to 3 per cent in murine typhus. It is practically nil in young children and very high in the aged.

The Spotted Fever Group.—The spotted fever group, in addition to Rocky Mountain spotted fever of the United States, includes *fièvre boutonneuse* of the Mediterranean countries, tropical typhus, type K of South Africa, and a Brazilian disease described under the name of São Paulo typhus. The etiologic agent is a rickettsia, *Dermacentroxenus rickettsi*. The clinical picture is similar to that of typhus, but the rash appears earlier (on the second to fifth days), is more hemorrhagic, appears first on the extremities, and involves the palms and soles. Clinical variations, such as the presence in *fièvre boutonneuse* of a local lesion at the portal of entry with regional lymphadenitis, are the result of strain variation. All diseases of this group are carried by ticks, and the rickettsiae are found in the cytoplasm and also in compact clusters in the nuclei of the cells of many tissues in ticks, including the salivary glands. Several varieties of ticks and several intermediate mammalian hosts are involved in the epidemiology of different varieties within this group. The mortality in different localities and from various strains ranges from 1 to 95 per cent.

Pathologically, the changes in spotted fever (Fig. 27) are much like those in typhus. Differential microscopic diagnosis can be made only by an experienced observer. Rickettsiae are found in the smooth muscle cells of arteriolar walls, while in typhus, the organisms are confined to the endothelium.

The Tsutsugamushi Group.—The tsutsugamushi group of diseases occurs in Japan, China, Sumatra, Australia, and several other countries and islands along the western Pacific coast. This group includes "mite typhus," which assumed military importance in World War II. The etiologic agent, *Rickettsia tsutsugamushi*, is carried by the larval form of the tropical mite (*Trombicula akamushi*). Tsutsugamushi

disease is an exanthematic febrile illness, often difficult to differentiate clinically from typhus and spotted fever. In most strains a necrotic lesion occurs at the site of attachment of the vector, together with regional lymphadenitis. In strains associated with a local lesion, the mortality is high (20 to 60 per cent), but in the absence of a local lesion the mortality is low. The disease has a reservoir in mice and other rodents, and one variety, "mite typhus," has recently been transmitted to mice and guinea pigs by the injection of blood from human patients.



Fig. 27.—Rocky Mountain spotted fever; showing the characteristic vascular pathology. A fibrin thrombus partially occludes the lumen of the vessel, and there is a focal perivascular collection of lymphocytes and macrophages. (Courtesy Dr. Henry Pinkerton.)



Fig. 28.—Focal brain lesions in tsutsugamushi disease, showing vascular origin and stages of development.

The pathologic changes are essentially like those in typhus and spotted fever, with the addition of mild rickettsial peritonitis, pleuritis, and pericarditis. Interstitial pneumonitis (Fig. 33), probably of rickettsial origin, is usually found but is often complicated by bacterial bronchopneumonia. The tendency for thrombosis to occur is much less than in typhus and spotted fever, and for this reason the rash does not become hemorrhagic, and resembles more the eruption seen in measles. The cerebral and myocardial lesions resemble those of typhus and spotted fever. (Figs. 28 and 29.)

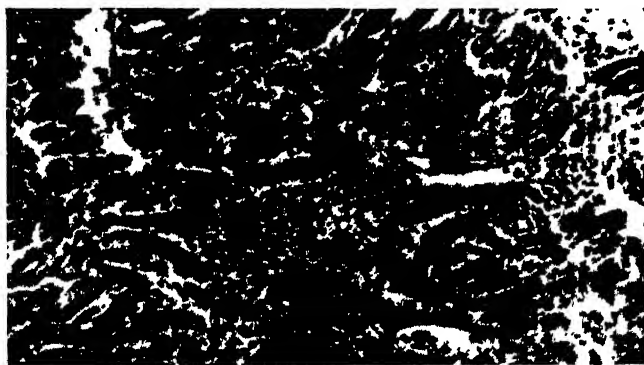


Fig. 29.—Interstitial myocarditis in a case of tsutsugamushi disease.

Q Fever.—A recently discovered disease, Australian Q fever, is probably identical with American Q fever which was discovered even more recently. The etiologic agent has been named *Rickettsia burneti* and *R. diaporica*, respectively by Australian and American workers. It is a facultative intracellular parasite, growing both intracellularly and extracellularly. The organism has been isolated from ticks in Montana. Unlike other rickettsiae it passes through porcelain filters. (This characteristic suggested the generic name *diaporica*). Clinically, there is usually no rash, but an atypical bronchopneumonia, discoverable at times only by x-ray examination, seems to be a constant finding. The epidemiology is not yet clear, but there is evidence that, unlike the other rickettsial diseases, direct transmission from person to person may occur without the intervention of an insect vector, and possibly by droplet infection. In fatal cases, the lungs show firm consolidation and microscopically an interstitial pneumonia, with inflammatory cells in the

alveolar walls, while the alveolar spaces contain fibrin with only a few mononuclear cells.

Trench Fever.—Trench fever is a louse-borne infection, which proved to be an important cause of disability in World War I, although it is never a fatal disease. It is characterized by recurrent attacks of fever, with severe pain in muscles, bones, and joints. An extracellular organism, named *Rickettsia wolhynica*, appears in the intestinal tract of lice after feeding on febrile patients. It is probably the cause of the disease, although failure to transmit the infection to experimental animals has made conclusive proof impossible. Nothing is known concerning the pathologic changes in this disease. It reappeared on a small scale during World War II.

Diagnosis of Rickettsial Diseases

The Weil-Felix reaction, carried out much like the Widal reaction in typhoid, is of value in the diagnosis of typhus, spotted fever, and tsutsugamushi disease. The antigens used are strains of *Bacillus proteus* isolated from patients. Although this organism is unrelated to the etiologic rickettsiae, agglutination occurs frequently in high titers, for some unknown reason. In typhus, agglutination in high titer with *B. proteus* OX19 is characteristically obtained, while in tsutsugamushi disease, the principal agglutinins are against *B. proteus* OXK. In spotted fever, agglutinins for both of the above strains are commonly present, but the titers are usually low.

Injection of guinea pigs with blood from suspected cases is often necessary for the accurate diagnosis of sporadic cases of typhus, spotted fever, and Q fever. Having established the strain in guinea pigs, cross-immunity tests with known strains are carried out.

Vaccination.—Although the rickettsiae refuse to grow on cell-free bacteriologic media, vaccines of undoubted value have been prepared against typhus, spotted fever, and Q fever. Of the various sources of rickettsiae, which include emulsified viscera of infected tissues of ticks and lice and media containing living or surviving infected mammalian cells, the infected yolk sac membrane of the developing chick embryo has proved most suitable for large scale production of vaccine. The rickettsiae grow freely in the cells lining the yolk sac, and are readily freed from their host cells and from the yolk to form the emulsion used for vaccination.

Bartonellosis (Carrion's Disease)

Carrion's disease is of considerable importance in Peru, Ecuador, Chile, and Colombia but has not been reported elsewhere. It is caused by a rickettsia-like organism, *Bartonella bacilliformis*, which is carried by sandflies. It occurs in two stages: an acute febrile anemia (Oroya fever) and a nodular cutaneous eruption (verruca peruana). The anemic stage is caused by the growth of the organism in the red blood cells. In severe cases, the red cell count falls rapidly and death occurs in a few days. The cutaneous eruption occurs during convalescence from the anemic stage, or may occur in individuals who have passed through a mild anemic stage without clinical illness, or with only mild illness.

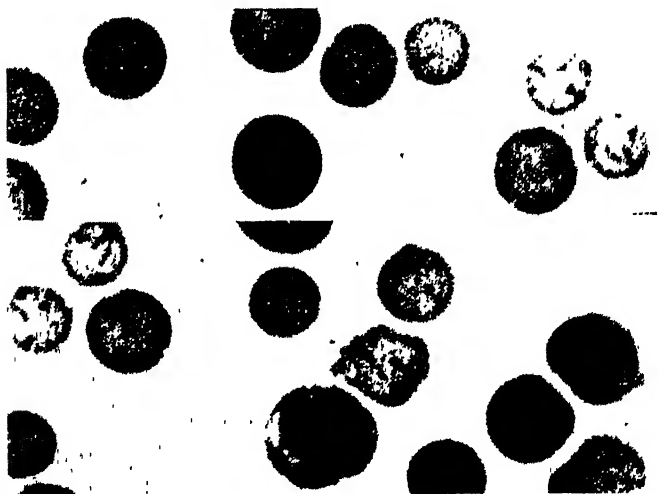


Fig. 30.—Oroya fever, showing bacillary and coccoid forms of *Bartonella bacilliformis* in the erythrocytes (Giemsa-stained blood film).

The organism, which grows in special cell-free media, is found in the cutaneous lesions as well as in the red blood cells. In fatal cases, not only the red cells, but the reticulo-endothelial cells in practically all organs are filled with organisms. The cutaneous lesions, microscopically, resemble rapidly growing hemangio-endotheliomas, but eventually heal without leaving scars. Diagnosis is made by finding the organism in red blood cells in giemsa-stained blood smears (Fig. 30) or by blood culture.

VIRAL DISEASES

The term virus, formerly used in the broad sense to mean merely "infective agent" is now restricted to filter-passing infective agents with certain characteristics which will be discussed below. Although filtrability depends on a number of factors other than the size of the particles, it is generally true that viruses pass through unglazed porcelain filters, while rickettsiae and bacteria do not.

In association with many viral infections, "inclusion bodies" are seen in the infected cells. The bodies occur either in the nucleus or in the cytoplasm. They vary considerably in shape and size, but usually are roughly spherical and their average size is about that of the erythrocyte. They tend to be eosinophilic with ordinary staining methods, and to be surrounded by a clear zone in the nucleoplasm or cytoplasm in which they are embedded.

Although several of the larger viruses are nearly as large as rickettsiae and some of the smaller bacteria, the smaller viruses approach molecular size (8 millimicrons). The larger viruses, like the rickettsiae, probably have some independent metabolic activity. The smaller viruses may be completely dependent on the enzymes of their host cells, and some of them may, like certain plant viruses, prove to be autocatalytic proteins, which can be crystallized and purified. In this case, although capable of reproduction in the sense that they increase in amount in infected tissues, it is difficult to regard them as living.

The inclusion bodies of several of the larger viruses, such as those of psittacosis and smallpox, are clusters of small rickettsia-like structures known as "elementary bodies" (Fig. 31). Such inclusions are granular in appearance when suitably stained. The inclusion bodies associated with the smaller viruses are homogeneous or coarsely vacuolated. They may be aggregates of elementary bodies, too small to be seen as individuals, or they may arise from the damaged cytoplasm or nucleoplasm of cells.

The important properties of viruses, in addition to their filtrability, are as follows: 1. Cytotropism. Viruses grow only within cells; often only within certain types of cells and in certain species of animals. They cannot be cultivated in cell-free media. They can be grown only in media containing living cells or in the membranes of the developing egg embryo. 2. The formation of inclusion bodies (see above). In many viral diseases, however, these structures are not seen. 3. Many

viruses lie dormant in tissues for long periods of time (latent infection), producing neither symptoms nor lesions. Under these conditions, however, a virus may be highly virulent for a host of a different species, or for its original host if resistance is lost. 4. Viruses, under certain conditions, undergo rapid variation. Yellow fever virus, for example, becomes neurotropic when infected intracerebrally in mice (see below). 5. Viral infections tend to pave the way for bacterial infection, which is often the true cause of death. 6. Immunity of high degree and long duration characteristically follows viral infections. Exceptions to this are the common cold, influenza, and herpes simplex. 7. Many viruses, like the rickettsiae and certain protozoa, are transmitted to man by insect vectors. 8. Viral infections in general do not respond to chemotherapeutic agents such as the sulfonamides and penicillin. This is probably due to their intracellular location and metabolic dependence on their host cells.

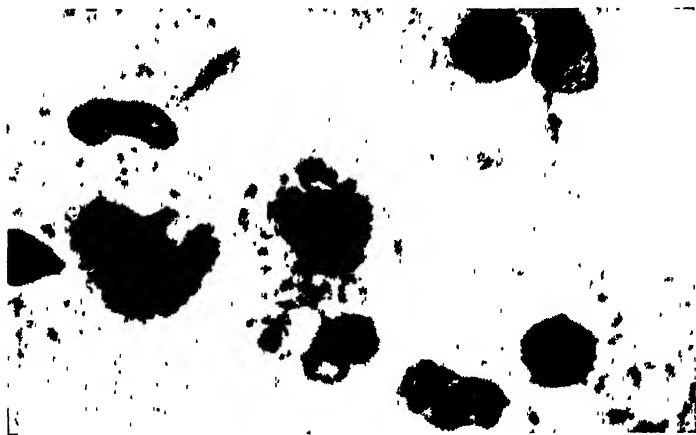


Fig. 31.—Psittacosis. Granular cytoplasmic inclusions composed of closely packed elementary bodies (from a tissue culture preparation).

The microscopic changes produced by viral infection are almost as varied as those produced by bacteria, ranging from acute necrosis to a proliferative, granulomatous reaction. Of particular interest is the fact that certain tumors of lower animals are apparently caused by viruses, notably the Rous chicken sarcoma, the Shope rabbit papilloma, and Lucké's carcinoma of the frog kidney. In the latter tumor nuclear inclusions are seen.

The field of viral diseases has expanded rapidly in recent years, as methods for the isolation, propagation, and study of the viruses have been devised. Many diseases now classed as of unknown etiology will no doubt prove to be of viral origin. For the isolation of viruses, the intracerebral or intranasal injection of mice and the intranasal injection of ferrets have proved particularly successful, but in certain viral diseases the monkey is the only animal which has been successfully injected. The propagation of viruses in tissue cultures and on the chorio-allantoic and yolk sac membranes of the chick embryo has also been of great value.

No satisfactory classification of viruses is available, because of our lack of knowledge concerning their biologic properties. They are identified largely by immunologic tests involving the use of known strains. On the basis of their tissue affinities, they are often classed as dermatropic, epitheliotropic, neurotropic, pantropic, etc. In this discussion, the viral diseases have been grouped arbitrarily according to the system in which the chief clinical manifestations are seen.

Viral Diseases of the Central Nervous System

General Considerations.—The viral diseases of the central nervous system (viral encephalitides) form a group of great clinical importance. In addition to those in which a viral etiology has been proved by transmission to experimental animals, there are several conditions of probable viral etiology.

Viruses produce a diffuse inflammation of brain and cord substance (encephalitis and myelitis) in contrast to bacteria, which cause either meningitis or localized abscesses. For the most part, the viruses develop within ganglion cells of the brain and cord. Nervous tissue responds to their presence by an acute inflammatory reaction, essentially like that in other tissues, but with certain special features. Since the lesions produced by different viruses have many histologic features in common, certain general types of lesion may first be described. Capillary congestion and petechial hemorrhages into the perivascular spaces and surrounding brain substance are common to most viral infections. The perivascular spaces take the place of lymphatics, which are absent in the brain. Accumulations of lymphocytes and plasma cells around blood vessels (perivascular cuffing) is another common type of lesion. Early degenerative changes in ganglion cells are difficult to recognize, but nuclear degeneration, especially when accompanied by the



PLATE IV.—Negri bodies of rabies. Van Gieson stain. (From Gradwohl, R. B. H.: Clinical Laboratory Methods and Diagnosis, St. Louis, The C. V. Mosby Company, 1938.)

accumulation of large mononuclear phagocytes around the damaged cells, is clear evidence of cell death. This phenomenon is called neuronophagia. The mononuclear phagocytes are derived from the microglial cells which are believed to be of mesenchymal origin, and members of the reticulo-endothelial system.

Focal collections of neuroglial cells (glial nodes) appear to be an attempt at repair and correspond to fibroblastic proliferation outside of the nervous system. Proliferation of capillary endothelium occurs much as it does in inflammatory lesions elsewhere. Focal areas of demyelination are the result of vascular occlusion.

Rabies.—Rabies is a viral disease, always fatal when untreated, which is usually acquired by the bite of a dog. The virus is introduced into the wound with the saliva and travels slowly along the peripheral nerves to reach the brain. The long incubation period, which may consume as much as nine months when the bite is on the lower extremities, allows time for preventive vaccination by the Pasteur method. The value of preventive vaccination is disputed by some authorities. In bites about the head, the incubation period may be only two or three weeks. When a dog suspected of having rabies has bitten a human being, the dog should be captured alive. If the dog has rabies, death will occur in a few days, and a positive diagnosis can be made by finding the characteristic inclusion bodies (Negri bodies) in the ganglion cells of the brain. Intracranial injection of emulsified dog brain into mice may give a positive diagnosis in some cases in which Negri bodies cannot be found.

Clinically the disease is manifested by muscular spasm, excitement, generalized convulsions, and eventual coma. The pathologic lesions are confined to the brain and spinal cord. Grossly no striking changes are seen. Microscopically there may be areas of petechial hemorrhage, perivascular accumulations of lymphocytes, and ganglion cell degeneration with the accumulation of phagocytic cells (neuronophagia). In the ganglion cells are found the pathognomonic Negri bodies (Plate IV). Often, however, the inflammatory reaction fails to occur, and the only evidence of the disease is the presence of these Negri bodies. Goodpasture believes that the Negri bodies are composed largely of degeneration products of the neurofibrillae, but other workers have thought that they are composed of elementary bodies. With ordinary staining methods, the Negri bodies appear homogenous or vacuolated rather than granular.

Poliomyelitis (Infantile Paralysis).—Poliomyelitis is an acute viral infection, in which the most important lesions are those involving the spinal cord. It is primarily a disease of children. The relative immunity of adults is probably the result of mild unrecognized or asymptomatic infections during childhood. During epidemics, which occur in the late summer and fall, many children who do not show paralysis suffer from mild upper respiratory or gastrointestinal symptoms, with or without minor neurologic findings. The virus may be isolated from the throat washings of such children. These mild or abortive cases are believed to be about six times as common as the cases with frank paralysis, and probably play an important part in the epidemiology of the disease. There is some evidence that apparently healthy people may act as carriers of the virus.

Experimentally, the disease may be transmitted to monkeys by intranasal injection of the virus, and it has been shown that the virus reaches the brain by passing along the olfactory nerves. The high concentration of the virus in human stools, however, and its isolation from sewage, suggest that under natural conditions the gastrointestinal route of infection may be more important than the respiratory route. Insect transmission of the disease is also regarded as a possibility, but has not been definitely established.

The frequent occurrence of poliomyelitis in large well-nourished children was stressed by early clinical observers. Recently it has been shown that undernourished or thiamine-deficient mice show a lower death rate from the disease than well-nourished mice. In monkeys, however, the course of the disease apparently is not influenced by dietary factors.

Clinically the disease is characterized by fever, malaise, headache, vomiting, and occasionally by neck rigidity. Spinal fluid examination usually shows 10-200 cells per cu. mm., with lymphocytes predominating, although neutrophils may be more conspicuous in the early stages. Within two to three days flaccid paralysis of the arms and legs commonly occurs. This lower motor neuron type of paralysis is due to necrosis of the ganglion cells in the anterior horns of the spinal cord. Involvement of the respiratory center leads to sudden death. In certain cases the brain is involved, giving a clinical picture suggesting encephalitis.

Grossly, the spinal cord and in the superior type, the brain stem and dentate nucleus may show edema and petechial hemorrhages. The microscopic lesion is essentially degeneration of the ganglion cells, which is usually best seen in the

anterior horns of the spinal cord. Intranuclear inclusions are said to be present in the ganglion cells in the early stages, but are not commonly seen in autopsy material. Ganglion cells show changes varying from nuclear degeneration and disappearance to complete lysis. Often the ganglion cells have largely disappeared. The various types of reaction described above—perivascular cuffing, petechial hemorrhage, neuronophagia, and glial nodes—are characteristically seen (Fig. 32). Neutrophils are usually present in considerable numbers, often in focal collections, and their presence is important in differentiating the superior type from encephalitis lethargica, since the inflammatory cells are practically all mononuclears in the latter disease.

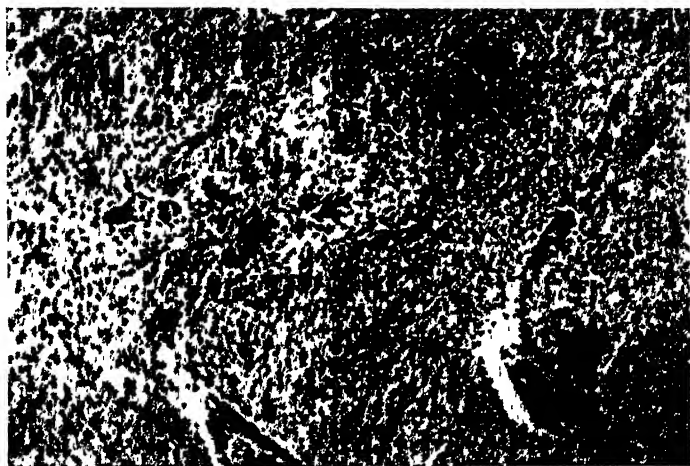


Fig. 32.—Acute poliomyelitis. Focal and diffuse collections of inflammatory cells, some of which are perivascular in position.

In recovered cases, the paralyzed muscles show atrophy and replacement by fatty tissue and connective tissue.

Epidemic Encephalitis.—Epidemic encephalitis, or encephalitis lethargica, is a disease of unknown etiology. The establishment of the viral etiology of St. Louis encephalitis, Japanese *B. encephalitis*, equine encephalomyelitis, and Australian X disease, all of which resemble epidemic encephalitis pathologically, is probably the most important reason for believing in the viral etiology of the latter disease. The herpes virus has been suspected of causing encephalitis

lethargica, but is rarely recovered by animal inoculation, and on the whole the evidence is far from conclusive.

The clinical picture is variable and is characterized by various combinations of somnolence, excitement, diplopia, and reflex changes. The mortality during the acute stage is 20 to 40 per cent. Lethargy may persist for many months. Dementia, permanent cranial nerve paralysis, and other neurologic symptoms may occur. Paralysis agitans, with slow speech, expressionless face, and pill-rolling tremor is a common sequela, even when the initial attack is mild. The spinal fluid, in the acute stage of the disease, shows a normal or slightly increased cell count, and neutrophils are absent.

The gross and microscopic lesions are, in general, similar to those of poliomyelitis except for their different distribution, less marked degeneration of ganglion cells, and the absence of neutrophils already commented on. Perivascular collections of lymphocytes are the most constant and conspicuous microscopic feature. Inclusion bodies have not been described.

St. Louis Encephalitis.—St. Louis encephalitis shows only minor clinical and pathologic differences from encephalitis lethargica, but is readily transmissible to mice by the intracerebral injection of brain tissue from fatal cases. Unfortunately, the virus cannot be recovered from spinal fluid by this method. Some evidence of mosquito transmission of this type of encephalitis has been obtained. The virus has been recovered from chicken mites.²³ Inclusion bodies have not been demonstrated. Serious sequelae of the type following encephalitis lethargica occur only rarely.

Equine Encephalomyelitis.—Equine encephalomyelitis is of particular interest as an example of a disease which was thoroughly studied in a lower animal (the horse) before there was reason to suspect its importance in human pathology. It occurs in two strains, the Eastern and Western, which only partially cross-immunize. The disease is immunologically distinct from St. Louis encephalitis and other known types of viral encephalitis. The pathologic lesions resemble those of encephalitis lethargica, but neutrophils are more prominent. The disease is almost certainly conveyed to man by mosquitoes. Inclusion bodies are not seen.

Lymphocytic Choriomeningitis.—Lymphocytic choriomeningitis is a recently recognized disease, characterized by headache, nausea, vomiting, and rigidity of the neck. It has a low mortality, and the pathologic picture in man has not been sufficiently studied. In mice and guinea pigs, which

are readily infected by the inoculation of spinal fluid from a human case, there is a marked lymphocytic reaction in the meninges, and interstitial pneumonia is also found.

Acute Disseminated (Postinfectious) Encephalomyelitis.—Acute disseminated encephalomyelitis occurs following certain infectious diseases, notably measles, mumps, smallpox, chicken pox, and vaccination, and also occurs spontaneously. Some workers believe that the viruses of the antecedent diseases are etiologically involved, but the evidence is far from conclusive.

Microscopically, most of the lesions described above as characteristic of the viral encephalitides are inconspicuous or absent, and the essential feature is extensive perivascular demyelination, best demonstrated by the Weigert stain. This stain colors the normal myelin sheaths black, and areas of demyelination stand out clearly.

This disease has not been transmitted to experimental animals, nor have inclusion bodies been demonstrated, so that there is considerable doubt concerning its true etiology. Somewhat similar demyelination of the central nervous system occurs in certain vitamin deficiencies.

Diagnosis of Viral Encephalitides.—The various types of viral encephalitis are difficult to distinguish from one another and from certain types of noninfectious encephalitis on purely clinical grounds. Accurate diagnosis must therefore be based upon isolation of the virus, or upon immunologic tests.

Unfortunately, the isolation of the neurotropic viruses in animals is usually possible only by the injection of brain material obtained post mortem. This method is of value in determining the nature of the virus involved in an epidemic. When the virus has been transmitted to mice, guinea pigs, or other experimental animals, cross-immunity tests with known strains may be carried out. In isolated nonfatal cases, the protection test is of greatest diagnostic importance. This test is carried out by mixing the blood serum of the patient with known viruses, and injecting the mixtures into animals. If such animals are protected against St. Louis encephalitis, for example, while the control animals react positively, a diagnosis of St. Louis encephalitis is justified.

As a result of the more frequent use of the method of animal inoculation in cases of encephalitis, the virus of lymphogranuloma has recently been established as an etiologic agent,²⁸ and it is probable that other viruses capable of producing encephalitis in man will be discovered.

Respiratory Viruses

General Considerations.—The lung, like the central nervous system, reacts to viral infections in a rather characteristic manner, so that the viral etiology of a pulmonary lesion may be strongly suspected from histologic evidence alone. Viral pneumonias are of the interstitial type (Fig. 33). Inflammatory cells are largely of the mononuclear variety, and accumulate chiefly in the alveolar walls and in the peribronchial and septal connective tissue. The alveolar lining cells, often undergo cuboidal metaplasia, and mitotic figures are seen in them. The alveoli either remain free from exudate or contain a serous or gelatinous exudate, with only a few inflammatory cells, chiefly mononuclears. Condensation of this exudate by inspired air often forms a hyaline eosinophilic membrane which lines the alveoli. These features, though suggestive, are not pathognomonic of viral infection since they occur in infections with other intracellular parasites (*Rickettsiae* and *Toxoplasma*) and probably in certain bacterial and allergic inflammations of the lung.

The damage inflicted by viruses often makes the lung susceptible to bacterial invasion. Secondary bacterial pneumonia, with its usual picture of exudation into the air spaces, is nearly always present in fatal cases, and may obscure the characteristic picture of the original viral pneumonia. There is evidence, for example, that a preceding infection of the lung with the influenza virus is of etiologic importance in certain epidemics of staphylococcal pneumonia (see p. 67).

Influenza.—Influenza is numerically the most important of the viral diseases; it is estimated that about 500,000,000 cases with 15,000,000 deaths occurred during the pandemic of 1918-1919. Smith, Andrews, and Laidlaw, in 1933, reproduced the disease in ferrets by the intranasal injection of filtered washings from the nose and throat of human cases, thus demonstrating the viral nature of disease. Mice are also susceptible, and the virus may be propagated in the fertile egg. Two antigenically different strains are known as types A and B. Vaccination against the disease has not proved successful because of the fact that immunity is of short duration.

Clinically the disease is a respiratory infection with fever, prostration, and muscular pains. Clinical diagnosis is difficult in sporadic mild cases. Reliable laboratory diagnosis can be made by isolating the virus in ferrets or in fertile eggs, or by demonstrating neutralizing antibodies in the blood of the patient. The observation that adult chicken erythrocytes

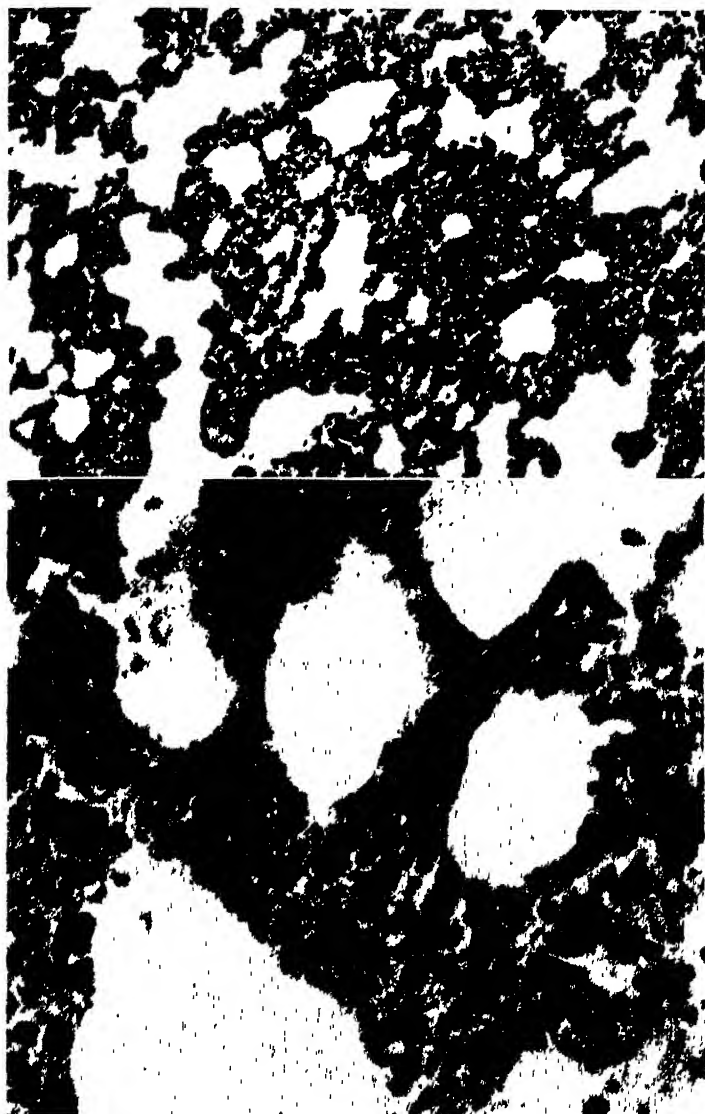


Fig. 33.—Interstitial pneumonia in a case of tsutsugamushi disease.

agglutinate in the presence of influenza virus²⁹ has greatly simplified both of these tests. If antibodies are present in the blood serum of the patient, they inhibit the agglutination of the chicken erythrocytes which takes place normally when known virus is mixed with them. In its uncomplicated form the disease lasts for only two or three days and recovery is rapid. Fatalities are due largely to bacterial pneumonia resulting from secondary infection with the influenza bacillus, pneumococci, streptococci, staphylococci, and other organisms. The conditions which initiate and terminate epidemics and pandemics are not known.

Pathologically influenza is characterized by an acute inflammation of the nasopharynx, trachea, and bronchioles, with necrosis and desquamation of the epithelial lining cells. Grossly, the lungs most frequently show patchy areas of firm deep red consolidation, giving the picture of hemorrhagic bronchopneumonia. Occasionally the picture is that of lobar pneumonia. Acute splenitis and other visceral changes characteristic of sepsis are seen. Alveolar emphysema is present in the less involved areas, and severe interstitial emphysema is occasionally seen, even spreading to the subcutaneous tissues in the neck (see p. 368).

Microscopically, the picture of viral pneumonia, as described above, is seen only in cases with early fatal termination, and is usually obscured by a superimposed purulent bacterial pneumonia. Often, however, the viral type of pneumonia may still be seen in the less involved areas. The pneumonic lesions during the pandemic of 1918-1919 showed a striking tendency to heal by organization rather than by resolution, probably because of severe damage to the alveolar lining cells. Inclusion bodies are not found in association with either human or experimental influenza.

Common Cold.—The common cold (coryza), like influenza, has been shown to be caused by a virus. Further similarity to influenza is seen in the fact that secondary bacterial invaders are responsible for the formation of mucopurulent exudate and for the distressing symptoms which appear after the first two or three days. Involvement is usually confined to the nasopharynx, pharynx, larynx, and trachea, and pneumonia is of rare occurrence. Immunity is of a very transient nature, perhaps partly because of the occurrence of immunologically different strains of the virus.

Pathologically, one sees hyperemia and swelling of the involved mucous membranes, with an exudate which is at first serous, but rapidly becomes mucopurulent with the advent

of secondary bacterial infection. Hyperplasia and increased secretion of the mucous glands may persist for many weeks after recovery. Involvement of the mucosa lining the accessory nasal sinuses may prolong the infection because of the imperfect drainage of these cavities. No definite inclusion bodies have been described in association with the common cold.

Psittacosis.—Psittacosis is acquired by inhalation of the virus present in dried urine and feces from infected birds. It has recently been shown that several birds other than those of the parrot family, including pigeons and the fulmar petrel (a sea gull) may harbor the virus and cause human infection. Since a number of closely related but not identical strains have been isolated from different species of birds, the more general name *ornithosis* has been proposed for the disease.³² Latently infected birds, without clinical evidence of illness, are known to be a source of danger. Since diagnosis is difficult in the absence of a history of contact with a sick bird, many unrecognized cases probably occur. The psittacosis virus may be responsible for some of the bronchopneumonias of atypical nature, which have been described in recent years. Cases of transmission from man to man have been recorded but appear to be rare.

Clinically, psittacosis is an acute febrile illness, with intense headache, and physical signs of an atypical pneumonia. Leucopenia, instead of the leucocytosis which accompanies bacterial pneumonia, is an important diagnostic feature.

Pathologically one finds splenomegaly and congestion and cloudy swelling of the viscera, as in any acute infection, but the characteristic changes are in the lungs. Here we find patchy pneumonic consolidation. Microscopically the picture is that of a viral pneumonia as distinguished from that of bacterial pneumonia. Mononuclears, rather than neutrophils, predominate, and the alveolar walls are thickened by the accumulation of inflammatory cells. The alveolar lining cells are stimulated and appear to have become cuboidal in type with frequent mitoses. The alveoli contain a rather gelatinous exudate, containing relatively few cells.

Spherical clusters of minute coccoid elementary bodies of rather characteristic appearance are found with great difficulty in sections of human lungs, but they are very conspicuous in the brain of mice following intracerebral injection of the virus (Fig. 31, p. 109).

A recent observation of interest is that lymphogranuloma venereum, which is associated with rather similar elementary bodies, is closely related immunologically to psittacosis.

Viral Pneumonias in Infants and Children.—In several types of pneumonia in infancy distinctive inclusion bodies characteristic of viral activity have been found. In none of the types has the virus been isolated. The so-called "inclusion disease" described by Farber and Wolbach³³ and others is often associated with whooping cough. It is characterized by large granular inclusions which distend the nuclei, and occasional smaller cytoplasmic inclusions. Goodpasture and his co-workers³⁴ have described a type with inclusions which fill, but do not distend, the nuclei. An epidemic variety has been reported by Adams,³⁵ in which only cytoplasmic inclusions are seen. The mortality in this type is about 20 per cent.



Fig. 34.—Cytoplasmic inclusion bodies in multinucleated cells lining pulmonary alveoli. Several faintly stained nuclear inclusions are also present (from a case of giant cell pneumonia).

Giant cell pneumonia, as described by Hecht in 1910, is a rare but distinctive pneumonia of infancy and childhood. It is an interstitial pneumonitis, the most important diagnostic feature being the formation of large multinucleated giant

cells by proliferation and fusion of cells which line alveoli, alveolar ducts, and bronchioles. Cytoplasmic inclusions, pleomorphic and often very large, are found in these cases, and also less numerous small nuclear inclusions. A similar histologic picture with similar inclusions is found in fatal early uncomplicated measles, and in canine distemper in animals.³⁶

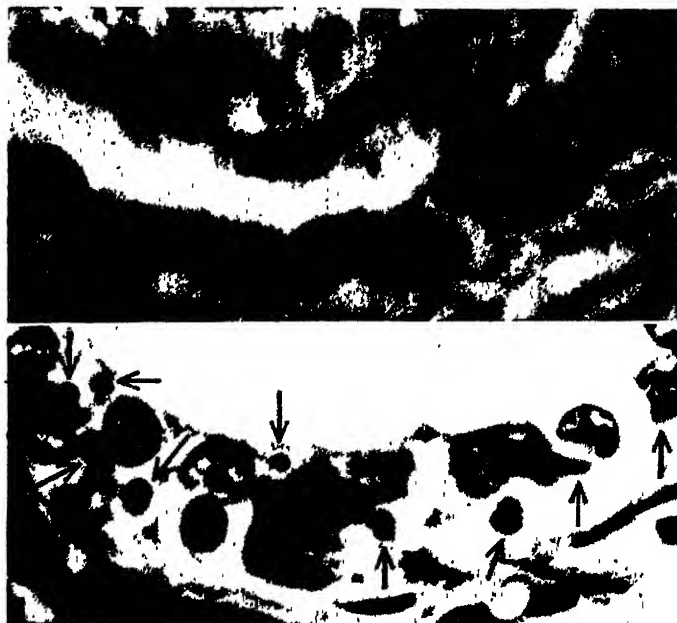


Fig. 35.—*Above*, Nuclear inclusion body in bronchiolar epithelium (from a case of giant cell pneumonia). *Below*, Cytoplasmic inclusion bodies in bile duct epithelium (canine distemper).

Primary Atypical Pneumonia.—This is an epidemic disease, with very low mortality, occurring chiefly in young adults. It has been of frequent occurrence in army camps. Clinically it is characterized by coryza, fever, sore throat, headache, and dry cough with little sputum. Leucopenia, rather than the leucocytosis which accompanies bacterial pneumonia, is the rule. Typable pneumococci are not found in the sputum. Roentgenograms show consolidation of the lung, spreading outward from the hilus.

Grossly, the lungs show patchy, deep red, firm consolidation. Microscopically the picture is that of an interstitial

pneumonia, with accumulation of mononuclear cells in the alveolar walls and peribronchial connective tissue. Cuboidal metaplasia of the alveolar lining cells and hyaline membrane formation are seen in some cases. The etiology of this condition is not yet clear. The term "virus pneumonia" has been applied to the condition, but "atypical pneumonia" seems preferable at the present time.

Cutaneous Viruses

Smallpox (Variola).—The etiologic agent of smallpox is characterized by its affinity for the epidermis. Transmission is either by direct contact or by droplet infection from the respiratory tract. The skin lesions begin as papules which later become vesicles, then pustules, and finally crusts. The lesions may be discrete, confluent, or hemorrhagic, the last type being practically always fatal. Healing with pitting of the skin is characteristic of the confluent form. A mild form of the disease, known as alastrim or parasmallpox, is also recognized. The historical aspects of vaccination with cowpox (*vaccinia*) are too well known to require discussion here.

Clinically the disease is characterized by severe headache and high fever. The fever usually subsides with the appearance of the papular skin lesions but returns with the vesicular and pustular stages of the lesion, at which time invasion by streptococci occurs.

The specific changes of smallpox are seen in the epithelial cells of the skin and mucous membranes. Typical inclusion bodies (Guarnieri bodies) are seen in the cytoplasm of these cells and also in nuclei. These inclusions, originally believed by Guarnieri to be protozoa, are now known to consist of closely packed elementary bodies, each having a diameter of about 0.2 micron. Goodpasture has named these bodies *Borreliota variolae hominis*. As a result of the presence of these bodies, the epithelial cells undergo degeneration. Vesiculation and pustule formation are not seen on mucous surfaces, probably because of the lack of a horny layer.

The fatal outcome of the infection is nearly always a result of streptococcal septicemia. The change of the skin lesion from a vesicle to a pustule corresponds to the period of invasion by streptococci. Lobar or bronchopneumonia is usually found at autopsy in fatal cases, the etiologic agent being most often a streptococcus or a pneumococcus. It is probable that this bacterial pneumonia is preceded by pneumonia of the viral type.

Chicken Pox (Varicella).—Chicken pox is a mild viral infection of childhood characterized by a typical skin eruption. Fatalities are exceedingly rare. The disease is acquired either by direct contact or through the upper respiratory tract. The cutaneous lesions are most numerous on the face and trunk, but eventually have a generalized distribution, often including the buccal and pharyngeal mucosa. They pass through the macular and papular stage, and become vesicular, with a surrounding bright red erythematous ring. Eventually crusts form, beneath which epithelial repair takes place. Fresh crops of lesions appear in the same skin areas on successive days, so that lesions in various stages of development may appear side by side. This is in contrast to the lesions of smallpox, which all evolve simultaneously.

Microscopic examination of the lesions shows congestion and edema of the corium, with mononuclear cell infiltration. Vesicles containing fluid are found in the epidermis. Nuclear inclusions which fill but do not distend the nuclei are found in many of the epidermal cells. These inclusions resemble those of herpes simplex, but the two viruses probably are not identical.

Herpes Simplex.—Herpes simplex is the common "cold sore" or "fever blister" which occurs most often on the lips, but may occur in the mouth (herpetic stomatitis), on the conjunctiva, or on the skin of the face or other regions. It may occur spontaneously, but most often appears during the course of some febrile illness. There is reason for believing that the virus often lies dormant in tissues, and is stimulated to produce lesions by some unknown mechanism which commonly acts in the presence of fever.

If vesicle fluid from a human lesion is rubbed into the scarified cornea of a rabbit, a specific viral conjunctivitis is produced. The virus is relatively large, and causes granular nuclear inclusion bodies which usually fill but do not distend the nuclei. Intracranial injection in mice causes an encephalitis which may be serially transmitted. The histologic resemblance of this encephalitis to encephalitis lethargica, together with the occasional recovery of herpes virus from normal human brain tissue, has suggested the possibility that this virus may be etiologically related to encephalitis lethargica. Rare cases of human encephalitis show nuclear inclusions resembling those of herpes, and even more rarely the herpes virus has been recovered from the brain in such cases.⁴⁰

Histologic examination of the vesicular lesions shows epithelial hyperplasia and necrosis, with vesicle formation. The nuclear inclusions already described are present in many of the epithelial cells.

Herpes Zoster.—Herpes zoster (shingles) is characterized by the formation of an erythematous and vesicular eruption along the course of sensory nerves. The lesions occur on the trunk or face, and are usually associated with pain, discomfort, fever, and malaise.

The cutaneous lesions show acidophilic nuclear inclusion bodies like those seen in herpes simplex. The basic lesion, however, is degeneration in the posterior root ganglia with associated perivascular mononuclear infiltration. In the process of healing, portions of the ganglia may be converted into scar tissue.

Although the presence of nuclear inclusions indicates the viral nature of herpes zoster, most attempts to isolate the virus in animals have been unsuccessful. Further study is needed to determine the exact relationship between the viruses of herpes zoster, herpes simplex, and chicken pox. It is probable that they are similar but not identical.

Measles (Rubeola).—Measles has been transmitted to monkeys, but not to other laboratory animals, and for this reason the study of its virus has been difficult. The virus also may be propagated on the chorio-allantoic membrane of the chick embryo, but gross lesions do not occur there. Attempts have been made to protect children against measles by the inoculation of virus attenuated by cultivation in the fertile egg. It is not yet possible to evaluate the results of these attempts.

Measles is highly communicable, and is spread chiefly by droplet infection through the upper respiratory tract. Clinically it is characterized by fever, cough, coryza, conjunctivitis, and a distinctive type of nonhemorrhagic macular rash which is most severe on the face, but involves the entire body. Koplik's spots, which are of early diagnostic significance, occur in the mouth, usually opposite the first molar teeth. They consist of minute, white flecks, formed by necrotic epithelial cells, and surrounded by a bluish areola, outside of which is a red areola.

The cutaneous lesions show vacuolar degeneration and eventual necrosis of the epithelial cells and marked perivascular lymphocytic infiltration, with endothelial proliferation in the capillaries, arterioles, and venules. The capillaries are markedly congested and occasionally rupture to form

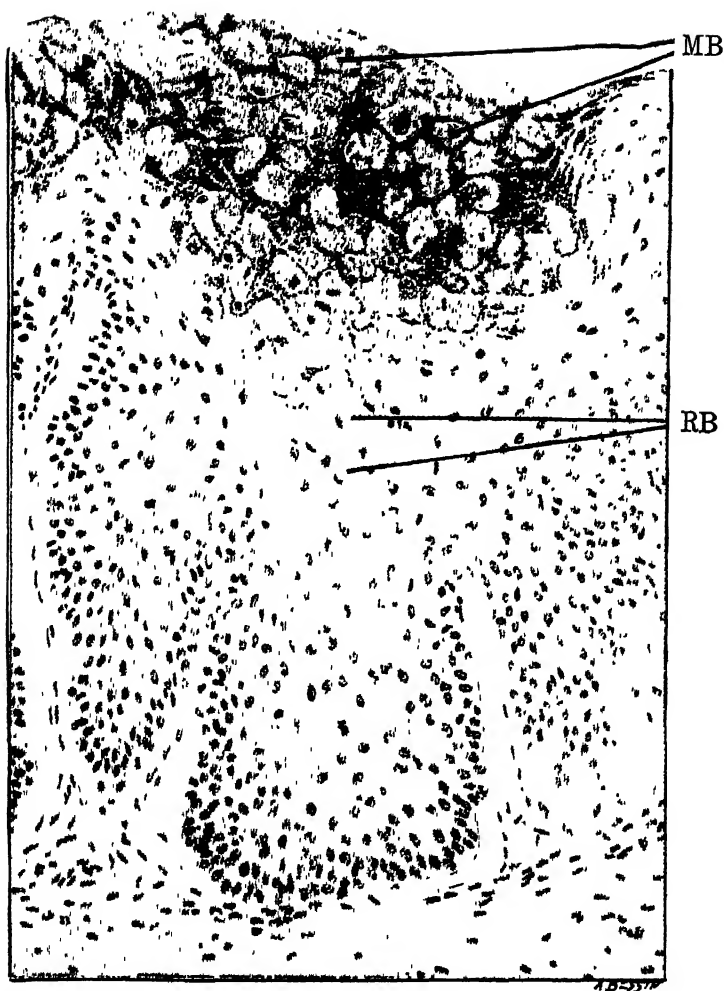


PLATE V.—*Molluscum contagiosum*. The rounded, hyaline molluscum bodies occupy the superficial portion of the epidermis. *RB*, Transformation of epithelial cells into round bodies. *MB*, Typical molluscum bodies. (From McCarthy, Lee: *Histopathology of Skin Diseases*, St. Louis, The C. V. Mosby Company, 1931.)

minute areas of hemorrhage in the corium. The Koplik's spots show an essentially similar picture.

In fatal cases, death is usually caused by bronchopneumonia. It is difficult to separate the lesions caused by bacterial pneumonia from those produced by the initial viral infection. Most fatalities occur late in the course of the disease, and although the bronchopneumonia seen then is often of the interstitial type, it has no particularly characteristic features. In patients dying early in the course of the illness, a peculiar type of pneumonia with giant cell formation and nuclear and cytoplasmic inclusions has been described³⁸ (see page 121).

In the lymphoid tissue of the tonsil and appendix large multinucleated cells have been observed in prodromal measles. Occasionally the finding of these giant cells in routine examination of surgically removed appendices has enabled the pathologist to make a diagnosis of measles before the appearance of the rash or Koplik's spots.

Diffuse encephalomyelitis, with demyelination of the white matter of the brain and cord, is occasionally seen in fatal cases which have shown clinical evidence of involvement of the central nervous system. Whether this lesion is caused by the virus of measles or by some other agent is not yet clear (see page 115).

Molluscum Contagiosum.—*Molluscum contagiosum* is a benign skin disease, characterized by the occurrence of raised, umbilicated, waxy cutaneous nodules. These lesions may be multiple, in which case the diagnosis is usually made clinically, or single, in which case the lesion may be suspected of being neoplastic and is often excised for diagnosis. The lesions heal spontaneously, usually after a few months, and are not associated with constitutional symptoms. The prickle cells of the epidermis undergo degeneration, with the development of rounded hyaline masses (molluscum bodies) in their cytoplasm. These eosinophilic inclusion bodies are aggregations of the minute elementary bodies of the virus (Plate V).

Miscellaneous Viral Infections

Mumps.—The virus of mumps has an affinity for the salivary glands and the testis (or ovary). The outstanding symptoms are painful swelling of the parotid gland and of the testicle. Orchitis is rare before puberty, but occurs in about one fifth of the cases in adults. The infection may be transmitted serially in monkeys by the injection of saliva

directly into Stensen's duct, but more convenient methods for the propagation of the virus have not been found.

Histologically, the parotid gland shows marked congestion and edema, catarrhal inflammation of the excretory duct, degenerative changes in the glandular epithelium, and leucocytic infiltration of the tubules and interstitial tissue. Repair takes place without permanent obstruction of the ducts or scar tissue formation. In the testis one finds a similar acute inflammatory reaction, probably dependent on primary injury to the tubular epithelium. Repair may be associated with a reduction in size of the affected testicle. Impotence and sterility are rare, since the condition is usually unilateral, and even when bilateral does not often cause enough permanent damage to interfere with normal function.

Meningo-encephalitis, manifested by the presence of an increased cell count in the spinal fluid, is often present without clinical symptoms. Occasionally, the clinical picture includes definite evidence of involvement of the central nervous system, which rarely results fatally. The etiologic relationship of the mumps virus to this meningo-encephalitis has not been determined definitely.

Yellow Fever.—Yellow fever is a highly fatal mosquito-borne viral disease of great clinical importance in the tropics, particularly in Africa and South America. The outstanding clinical features are fever, severe jaundice, hematemesis, hemorrhage into the gastrointestinal tract, hematuria, and evidences of severe renal damage, including uremia in fatal cases. Unfortunately, the control of the mosquito vector, *Aedes aegypti*, does not offer the promise of eradicating the disease, since there is evidence of a reservoir in monkeys and perhaps other wild jungle animals. There is also reason to believe that insect or arthropod vectors other than the *aegypti* mosquito may transmit the disease. The endemic form of the disease in South America is called "jungle yellow fever."

The virus injected into monkeys reproduces quite accurately the human disease, in which liver necrosis is the outstanding feature. Theiler showed that the virus, when injected intracerebrally in young mice, causes an encephalitis which is serially transmissible. Under these conditions, the virus changes to a neurotropic form, which is no longer capable of causing typical yellow fever in monkeys. This is a classical example of mutation or variation in a virus. Although no longer capable of producing illness, this modified virus when injected into monkeys or human beings, produces

strong immunity against yellow fever. Human vaccination at present is carried out by injecting virus which has been modified by cultivation in media containing minced mammalian embryonic tissue.

Post-mortem examination shows hemorrhage into the gastrointestinal tract, a yellow liver, often mottled with red areas, pale swollen kidneys, and a friable dark red spleen. Microscopically there is extensive necrosis of liver tissue with fatty infiltration which has a definite mid-zonal distribution. The damaged liver cells appear swollen, eosinophilic, and finely granular, with intracytoplasmic hyaline areas (Councilman bodies). Nuclear inclusions, less prominent and less easy to recognize than those of other viral infections, are often found in human liver, and almost constantly in fatal yellow fever in the monkey. This type of inclusion forms a rather irregular diffuse eosinophilic ring around the nucleolus. The necrosis of liver cells is so extensive that one might expect repair by fibrous tissue, but hepatic cirrhosis as a sequella of yellow fever has not been reported. Interference with prothrombin formation as a result of the hepatic damage probably explains the tendency for hemorrhage to occur.

In the kidneys, severe degeneration of the tubular epithelium is found. Other lesions which have been described include myocardial degeneration, and petechial hemorrhages in the brain, as well as on serous surfaces.

Trachoma.—The viral etiology of trachoma has gained acceptance slowly because of the difficulties involved in isolating the virus in animals and in demonstrating its presence histologically. In film preparations from the infected conjunctiva, spherical clusters of coccoid elementary bodies are commonly found in the cytoplasm of the epithelial cells. The cytologic picture somewhat resembles that seen in psittacosis and lymphogranuloma venereum. The disease can be reproduced in the monkey.

The lesions are confined to the eye, where the picture is that of a chronic granular conjunctivitis, with a predominantly mononuclear reaction. The granular elevations are foci of lymphocytic infiltration, or even actual lymph follicle formation. Healing by scar tissue with pannus formation often results in blindness.

Inclusion blenorrhea and swimming-pool conjunctivitis have a cytologic picture similar to that of trachoma, but recovery takes place without complications.

Epidemic Keratoconjunctivitis.—Epidemic keratoconjunctivitis is a recently recognized viral infection which causes

redness and swelling of the conjunctiva. Scrapings from the conjunctiva show inflammatory cells of the mononuclear type. Inclusion bodies have not been described, but the virus has been isolated by intracerebral injection into mice. The nature of the virus has not yet been determined. Recovery takes place in a few days or weeks, but in some cases there is residual impairment of vision as a result of corneal involvement.

Dengue.—Dengue (break-bone fever) is a rarely fatal febrile disease transmitted by the *Aedes aegypti* mosquito. Clinically there is fever, leukopenia, a mild inconstant rash, and severe pains in the joints and muscles. Transmission from person to person by the injection of filtered blood is possible, and there is evidence that unapparent infection may be produced in guinea pigs. Little is known concerning the pathologic changes in the condition.

Pappataci fever clinically resembles dengue, but is transmitted by the sand fly *Phlebotomus papatasi*. A rash does not occur in this disease.

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CHAPTER VII

SPIROCHETAL AND VENEREAL DISEASES

SYPHILIS

Syphilis, due to a spirochete, the *Treponema pallidum*, is the most important of the venereal diseases. It causes disability and death mainly from involvement of the heart, blood vessels, and nervous system, but any organ may be affected. The clinical manifestations are extremely variable, and latent periods occur in which there are no clinical signs other than positive serologic reactions (Wassermann and Kahn tests, etc.). The course of the disease is described in three stages. The characteristic lesion of the primary stage (chancre) is a hard ulcer which develops at the point of entrance of the organisms, and hence is usually on the genitalia. The secondary stage, developing about six weeks after the chancre, is characterized by maculopapular skin rashes, mucous patches on the oral mucosa, and generalized slight lymph node enlargement. Tertiary lesions develop after a latent period of months or years. They may be localized areas of coagulative gummy necrosis (gumma) or a chronic granulomatous inflammation with gradual destruction of tissue and development of fibrosis. This latter type of reaction is more common.

In contrast with the varied clinical and gross manifestations of syphilis, the microscopic features are relatively simple and constant, but rarely pathognomonic. Lesions of the skin in any stage of syphilis may show marked and irregular epithelial hyperplasia, simulating a cancerous change (pseudocarcinomatous hyperplasia).¹ The inflammatory cells in syphilitic lesions are predominantly lymphocytes and plasma cells, situated around small blood vessels and later more diffusely spread throughout the tissue. Fibroblastic proliferation and fibrosis accompany the process. Small blood vessels in syphilitic lesions exhibit changes, frequently an intimal thickening (endarteritis) and luminal narrowing or obstruction. This vascular change and consequent ischemia are a causative factor in the coagulation necrosis of the gumma. Final proof of the syphilitic nature of a lesion depends upon demonstration of the spirochete. Spirochetes are numerous in primary and secondary lesions, but scarce in tertiary lesions.

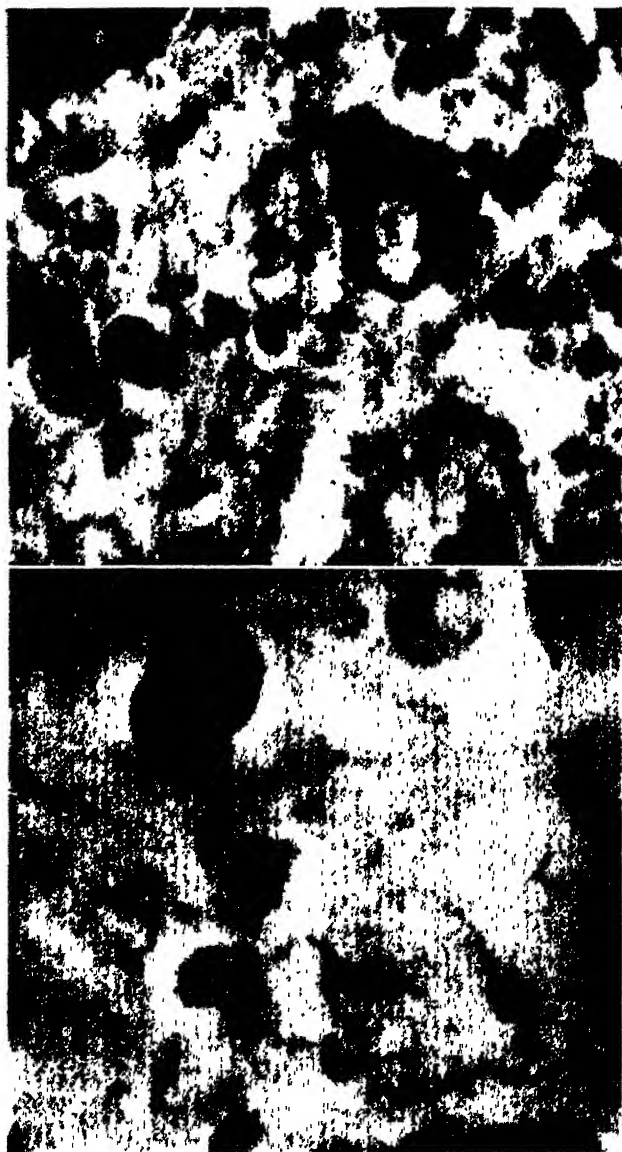


Fig. 36.—Spirochetes of congenital syphilis in the liver. Levaditi stain.

The *Treponema pallidum* (*Spirochaeta pallida*) is a slender organism, 5 to 15 microns in length—i.e., usually about once or twice the diameter of a red blood cell. It is characterized by its thinness, and the closeness and regularity of its corkscrew-like spirals, which average about 12 in number. It is stained only with great difficulty and is best demonstrated in smears from syphilitic lesions by dark-field examination, or against a black background of India ink. In tissues, it may be demonstrated by Levaditi's method, or some modification of it, in which the spirochete is impregnated with silver. Methods for their staining in tissues are technically difficult and uncertain.

Primary Stage of Syphilis.—The chancre or primary syphilitic lesion appears at the point of inoculation of the spirochete after an incubation period of one to four weeks. An abrasion of skin or mucosa facilitates entry of the organism, but probably is unnecessary for penetration of the genital mucosa. The chancre is on the genitalia in more than 90 per cent of cases, the next most common location being the lips or mouth. In 20 per cent or more of cases no primary lesion develops, or it is hidden in urethra or vagina and passes unnoticed. Syphilis has been transferred by blood transfusion, the spirochete being directly inoculated with the donor's blood. In such cases there is no primary lesion.

Very soon after penetration the organism becomes widely distributed in tissues and lymphatics. Hence prophylactic treatment must be very soon after exposure.

After an incubation period of about three weeks, the chancre begins as a thickening and hardening of the surface tissue. The epithelium of this area becomes necrotic, and sloughs off, leaving a shallow ulcer a few millimeters to a centimeter in diameter. The ulcer is single, round, and characterized by painlessness and hardness. The induration extends to form a flat, hard mass, which exudes clear serum but no pus. Secondary infection may occur and change the characteristic features. Histologically, the lesion shows fairly dense granulation tissue, with many small vessels and an infiltration of lymphocytes and plasma cells. These chronic inflammatory cells at first surround the small blood vessels but later spread out and become diffuse. The hardness of the lesion results from connective tissue formation and the accumulation of inflammatory cells. Necrosis is absent except on the surface. Secondary infection may

change the histologic picture. There is nothing absolutely characteristic about the lesion, and certain diagnosis depends on demonstration of the abundant spirochetes.

The chancre heals in three to eight weeks. The induration disappears, the area is recovered by epithelium, and healing leaves but slight fibrosis or scarring. The Wassermann reaction usually becomes positive about one or two weeks after the appearance of the chancre.

TABLE IV
SPIROCHETAL DISEASES

DISEASE	SPIROCHETE	MORPHOLOGY OF SPIROCHETE	MAIN FEATURES OF DISEASE
Syphilis	<i>Treponema pallidum</i>	5 to 15 microns, about 12 slender tightly wound regular coils	Venereal, widespread
Yaws (Frambesia)	<i>Treponema pertenue</i>	Resembles <i>Treponema pallidum</i> but coils not as regular or close, and body thicker	Nonvenereal. Lesions and stages similar to syphilis
Pinta	<i>Treponema carateum</i>	Indistinguishable from <i>Treponema pallidum</i>	Nonvenereal. Bluish pigmented and depigmented areas of skin
Relapsing fever	<i>Borrelia recurrentis</i> <i>Borrelia duttoni</i>	Large curving organisms, easily stained, 7 to 20 microns	Spread by lice, ticks, and other parasites. Organism found in blood smears.
Spirochetal Jaundice (Weil's disease) Spirochetosis icterohemorrhagica	<i>Leptospira icterohemorrhagiae</i>	6 to 15 microns long, fine tightly wound spirals enclosing an axial filament, prolonged to form straight or hooked ends	Hemorrhages in various organs, particularly lungs. Necrosis in liver and kidney. Spirochetes excreted in urine
Vincent's Angina	<i>Borrelia vincentii</i>	Large coarse organisms, many with pointed ends. Constantly found with long fusiform bacilli (<i>B. fusiformis</i>)	A symbiotic infection, associated with gangrenous and sloughing lesions of mouth, throat, and respiratory tract
Ratbite fever (Sodoku)	<i>Spirillum minus</i>	Broad, spiral organism 2 to 5 microns, regular spirals, blunt ends with flagellae	Febrile infection due to bite of infected rat. Primary lesion at point of inoculation, and recurring chills and fever. Spirochete may be demonstrated in blood

With development of the chancre the regional lymph nodes (usually inguinal) become enlarged, firm, and shotty, but are not painful. In the enlarged nodes there is hyperplasia of the cells lining the sinuses, which are filled with mononuclear cells. Small areas of focal necrosis may occur, but there is no tendency for the glands to suppurate.

Secondary Stage of Syphilis.—Secondary lesions appear six to ten weeks after the development of the chancre and are characterized by simultaneous appearance over the whole body, insignificant tissue reaction with little tissue destruction, and richness in organisms. The Wassermann reaction is almost invariably positive and is most dependable during this stage.



Fig. 37.—Gumma of testis. (Courtesy Dr. H. C. Schmeisser.)

During the incubation period and the period of the chancre, spread has occurred throughout the whole body by lymphatics and blood stream. Multiplication in these new foci results in the breaking out of innumerable lesions. On the skin, they most commonly take the form of a flat red (macular) or raised (papular) rash, but any type of skin eruption may be imitated. Sore throat is common, and elevated, white "mucous patches" involve the oral mucosa. There is a gen-

eralized slight lymph node enlargement, the glands being hard, discrete, and shotty. Histologically, the lymph nodes may show marked follicular hyperplasia, simulating giant follicular lymphadenopathy.² Flat condylomas (condyloma latum) develop in moist areas about the genitals or anus. These are broad lobulated elevations in which epithelial overgrowth is a marked feature.

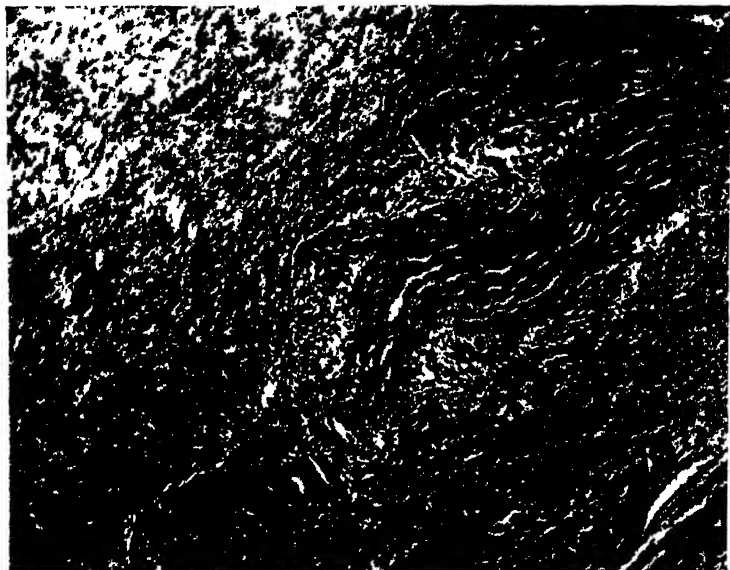


Fig. 38.—Syphilitic aortitis. Small area of gummatous necrosis in the media.

In all secondary lesions, the histologic change is essentially a perivascular accumulation of lymphocytes and plasma cells, with varying amounts of vascular dilatation and congestion. In macular lesions, cells are few in number. In papular lesions, cells are numerous in deep layers of the epithelium and in the corium. Secondary infection may produce pustular lesions, but as a rule tissue destruction is absent. The epithelium shows little change except in the condylomas, where papillomatous overgrowth may be marked. Healing occurs without scars. Milder recurrences of secondary lesions, separated by latent periods of apparent health, are the usual course.

The Tertiary Stage of Syphilis.—Between secondary and tertiary lesions there occurs a latent period of a few months to five or as long as twenty years. During this period the individual appears well, and the presence of active syphilis is recognizable only by serologic tests. Nevertheless, during this period there progresses a slow, mild, chronic inflammation in various invaded tissues, particularly the cardiovascular system or nervous system. This slow destruction and fibrosis may lead to eventual functional breakdown or may be evident only by gross or microscopic examination after death of the individual.

Gumma is a less common type of tertiary lesion, characterized by great destruction of tissue, and relatively few organisms. The gumma may be found in almost any organ or tissue. It is usually a solitary nodule of necrotic tissue, varying from microscopic size to a diameter of several centimeters. The opaque necrotic material has an elastic or "gummy" consistence. Microscopically, it presents a coagulative necrosis, somewhat like that of an infarction. About the necrotic material is a margin of lymphocytes and mononuclear cells. Multinucleated giant cells are rarely present. Proliferation of connective tissue cells encapsulates the lesion, and vascularized connective tissue may extend a considerable distance from the necrotic center. Differences between gummas and tubercles are outlined in Table V, but histologic differentiation of single lesions is not always possible without demonstration of organisms. The history of associated lesions usually must be considered in diagnosis.

TABLE V

DIFFERENTIAL FEATURES OF GUMMAS AND TUBERCLES

	GUMMA	TUBERCLE
Giant cells	Rare	Common
Epithelioid cells	Less numerous	More numerous
Lymphocytes and plasma cells	More numerous	Less numerous
Tissue structure	Often still visible	Completely obliterated
Fibroblasts	May be found in center of gumma	Absent from necrotic area
Blood vessels	Sometimes present	Absent
Size	May be several cm. in diameter	Rarely large
Number	Frequently single	Rarely single

When a gumma involves skin or mucous membrane, there is sloughing of necrotic material, so that an ulcer results.

Gummatous ulcers have irregular sharp walls, a punched-out appearance, and an irregular base. The palate is a common site and may be completely perforated. Gummas heal with absorption of the necrotic material, and formation of dense fibrous distorting scars. This distortion is particularly well seen in the liver, where deep contracted scars produce a peculiar lobed cirrhotic appearance (*hepar lobatum*).

Occasionally there is involvement by numerous miliary gummas, which begin as the usual perivascular involvement, but in which necrosis is slight or never complete. Healing occurs with diffuse and irregular fibrosis of the tissue.

As syphilis may affect practically any organ or tissue, only the more important are considered here.



Fig. 39.—Syphilitic aortitis. Note the longitudinal striation and tree-bark appearance. (Courtesy Dr. H. C. Schmeisser.)

CIRCULATORY SYSTEM.—The aorta is involved more commonly than any other organ, probably in every case of active syphilis. It is especially the ascending aorta and arch which are affected, parts which possess a particularly rich lymph supply. This distribution is in contrast to that of atherosclerosis, which most markedly involves the lower abdominal portion. All layers are affected. The adventitia shows perivascular collections of lymphocytes and plasma cells and later is scarred and thickened. The most important damage is to the media, where destruction of elastic and connective tissue fibers so weakens the wall as to allow

aneurysmal bulging. Nearly all true aneurysms of the aorta are of syphilitic origin. The intima is involved by an irregular fibrous thickening, which appears as an irregular wrinkling and pitting. The resulting "tree-bark" appearance is grossly characteristic. The intimal change causes little functional damage, except when it involves the sinuses of Valsalva, where it may result in narrowing or occlusion of coronary openings. Similar syphilitic lesions less commonly involve other arteries, also with aneurysm formation. Proximal portions of the coronaries may be stenosed or obliterated by syphilitic endarteritis.

HEART.—Syphilis may involve the region of the aortic valve, and probably the myocardium. Changes in the aortic valves may be dilatation of the aortic ring, thickening and shortening of the valve leaflets, or fusion of the valve leaflets into the wall of the aorta at their angles of attachment. These three types of change, which may occur singly or in combination, all produce insufficiency of the aortic valve. The extra burden of diastolic regurgitation into the left ventricle causes a work hypertrophy of that part.

The myocardium may be affected by narrowing or occlusion of the proximal portions or openings of the coronaries.³ In addition, Warthin has described a specific syphilitic involvement of the myocardium, characterized by interstitial infiltrations of lymphocytes and plasma cells along vessels. These patchy or diffuse lesions in later stages show only fibrosis. Conducting bundles may be involved and give rise to heart block. The frequency and importance of syphilitic myocarditis are still matters of dispute.^{4, 5, 6}

NERVOUS SYSTEM.—Luetic involvement of the nervous system may take the form of a meningo-encephalitis,⁷ general paresis (dementia paralytica), or tabes dorsalis (locomotor ataxia). Also, a gumma may develop in any part of the brain and simulate a tumor in its manifestations.

The meningeal involvement is a granulomatous meningitis, with marked thickening and adherence of all layers. The tissues are infiltrated with lymphocytes and, in older lesions, many large mononuclears. The blood vessels are involved and perivascular infiltration and fibrosis give rise to the meningeal thickening. Varying degrees of degeneration of underlying nerve cells accompany the meningitis.

General paresis is usually a late manifestation of syphilis. Treponemas have been demonstrated in the involved tissue. The disease is manifested by dissolution of mental powers and balance and finally complete insanity. Varying degrees

of atrophic change affect the cerebral convolutions, and there is usually some accompanying meningeal involvement with thickening and adhesions. Microscopic changes include degeneration of nerve cells and fibers in the cerebral cortex, especially in the frontal region, and proliferation of cortical neuroglia. Collections of plasma cells and lymphocytes are present about blood vessels. Storage in the microglia of a large amount of iron-containing substance, which gives a Prussian-blue reaction, is a most characteristic finding.

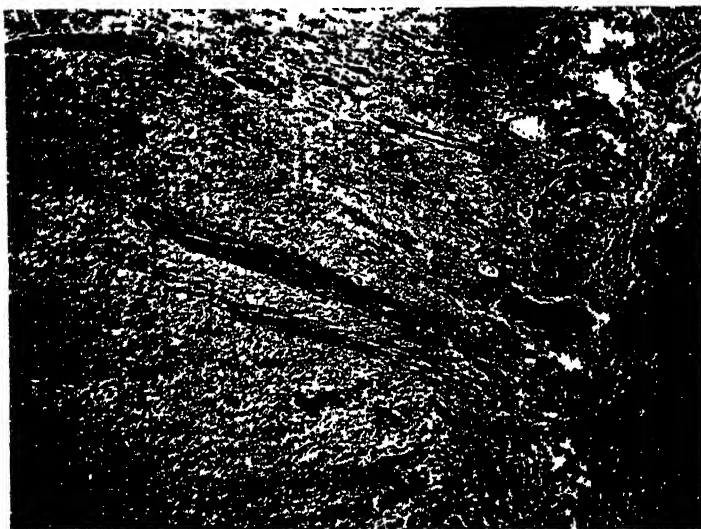


Fig. 40.—Syphilitic meningoencephalitis. The inflammatory exudate is extending into cerebral tissue, particularly around vascular spaces.

Tabes dorsalis (locomotor ataxia) is characterized by a degeneration and fibrosis of the posterior roots and posterior columns of the spinal cord, as a result of syphilitic inflammation. Injury to the nerve fibers has been attributed to meningitis, to direct inflammation, to a toxin and to presence of the spirochete itself. Varying degrees of meningeal inflammation and thickening accompany the cord changes. Occasionally the lateral pyramidal tracts and cranial sensory nerves are also involved. The changes are usually most pronounced in the lumbar portion of the cord. The posterior columns are shrunk and retracted, and pale gray on the

TABLE VI
THE COURSE OF SYPHILIS

STAGE	TIME	LESIONS	PATHOLOGIC BACKGROUND	RESULT
Incubation period	Average 3 weeks	No clinical signs	Reproduction of organisms locally at site of inoculation, and widespread distribution throughout body	Development of chancre
<i>Primary</i>	6 weeks	Chancre Local lymph node enlargement	Hard ulcerative lesion at point of inoculation, with many organisms. Wassermann becomes positive	Heals spontaneously. Slight scarring
<i>Secondary</i>	1-3 years. Latent periods and recurrences	Eruptive lesions on skin and mucous membranes. Generalized lymph node enlargement	Localized areas of congestion with perivascular round-cell infiltrations. Minimal tissue destruction. Lesions rich in spirochetes and highly infective. Wassermann positive	Heals spontaneously with minimal scarring
Latent periods	6 months-20 years	Present but not evident clinically	Progressive destruction of parenchymatous tissue and replacement by scar tissue, producing eventual functional breakdown. Wassermann may be positive or negative	Partial healing with fibrosis, producing functional and anatomic disturbances of organs
<i>Tertiary</i>	Lasts remainder of life	Chronic destructive fibrosing lesions or (and) gummas may involve any organ. Aortic endocarditis with regurgitation, myocarditis, aneurysm, meningoencephalitis, general paralysis, tabes		

cut surface. In these degenerated areas axons and myelin sheaths have disappeared, and there is increased neuroglial tissue. Occasionally there is round-cell infiltration or even small gummas where the posterior roots penetrate the arachnoid.

Congenital Syphilis.—Syphilis is frequently congenital, but it is not hereditary. Placental and fetal tissues are a particularly good soil for growth of the spirochete, and congenital infection probably occurs whenever the mother has

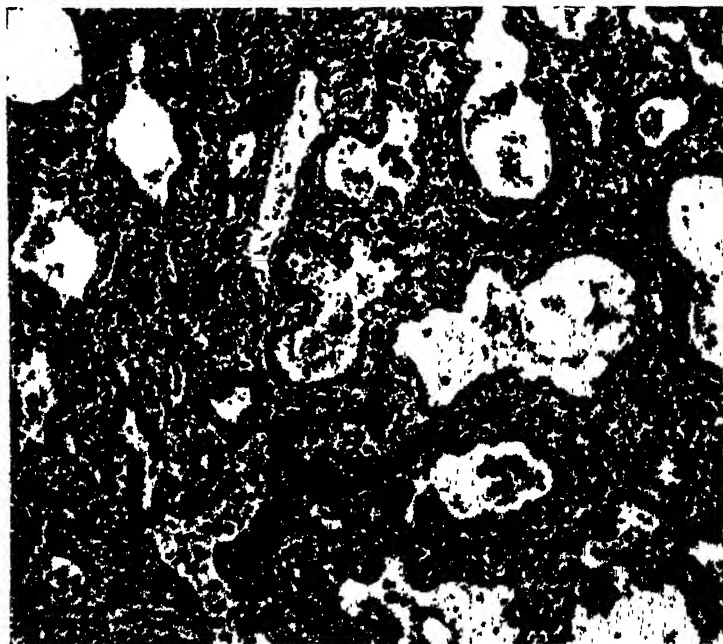


Fig. 41.—Pneumonia alba. Interstitial pneumonia in an infant with congenital syphilis. Note the cuboidal cells lining the gland-like alveolar spaces.

active luetic infection. The maternal infection may be old, and clinically latent, or may have been acquired just before or during pregnancy. Infection of the fetus may result in death in utero and abortion, in premature labor and still-birth, or in a live child with active syphilitic lesions. In some cases the child appears well at birth, but later develops evidence of syphilis (*lues tarda*). The old laws of Colles

and Profeta, to the effect that a healthy mother cannot be infected by her syphilitic child, and vice versa, are now known to be untrue. In all cases both mother and child harbor the infection, though in either one it may be clinically latent.



Fig. 42.—Placenta in syphilis, showing connective tissue thickening of villi with thickened fibrotic central vessels. (From Douglass and Faulkner: *Essentials of Obstetrical and Gynecological Pathology*, The C. V. Mosby Co.)

The placenta of a syphilitic infant is abnormally large. It often shows changes due to the infection, but not frequently so marked as to be diagnostic. Thickening of the

intima and adventitia of the vessels of the placenta and umbilical cord, and enlargement of the villi by new connective tissue formation about the central blood vessels, have been ascribed to syphilis.

Syphilitic infants born dead or dying shortly after birth frequently show skin lesions. These are usually in the form of blebs or bullae on the hands and feet. The infant appears small and undernourished, but the liver and spleen are enlarged.

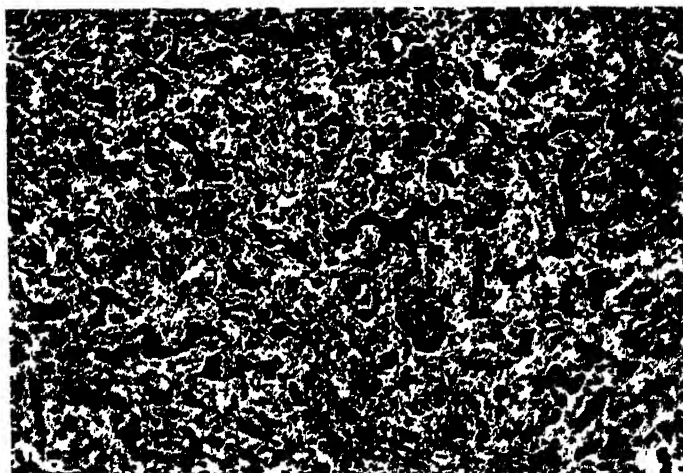


Fig. 43.—Fibrosis of the liver in congenital syphilis.

The main changes are delayed or faulty development of organs, which appear enlarged, dense, and fibrous. The lung, liver, spleen, pancreas, and kidney are frequently involved. The change in the lung is commonly called white pneumonia (*pneumonia alba*). The pulmonary alveoli are not fully developed, being lined by cubical epithelial cells, and their walls greatly thickened by fine connective tissue and small round mesoblastic cells. In the enlarged liver there is an increase of connective tissue, particularly around portal areas. Focal areas of gummatous necrosis and many focal collections of small, round, dark, blood-forming cells occur. Similar excess hematopoietic activity is evident in the spleen. Fibrosis or undifferentiated mesoblastic tissue is also prominent in the pancreas and kidney. In the latter

organ a prominent neogenic zone at the outer edge of the cortex indicates the delayed development.

Osteochondritis is the most constant lesion of congenital syphilis. It may be the sole lesion and is a valuable aid in roentgenologic diagnosis. In long bones the line of ossification between cartilage and bone is wide, irregular, yellowish and opaque, instead of a normal thin even gray translucent line. There is irregular and incomplete ossification in this area, with development of a cellular granulation tissue. Osteoblastic activity is diminished, with disturbance of normal resorption and alteration in the growth of cartilage. Periostitis with thickening frequently accompanies the osteochondritis, but seldom occurs alone.

Later forms of congenital syphilis produce various scars and deformities, some of which are characteristic stigmas of the disease. These include radiating scars about the mouth (rhagades), gummatous destruction of the nasal bones (saddle nose), and bulbous or tapered incisors with a notch in the center of the biting edge (Hutchinson's teeth). Interstitial keratitis producing corneal opacity also occurs.

OTHER SPIROCHETAL DISEASES

Yaws (Frambesia).—Yaws is a tropical disease, closely similar to syphilis, and due to a spirochete, *Treponema pertenue*, which is practically indistinguishable from the luetic spirochete. In yaws the Wassermann reaction is positive, and salvarsan treatment is effective. Yaws is not a venereal disease, and spreads by direct contact, mainly to children. An initial primary lesion develops at the point of inoculation, usually on a leg or arm, followed later by generalized scattered scaly macules. These go on to the development of vesicular and pustular elevations (frambesiomas). The initial lesion has marked epithelial hyperplasia, with lymphocytes and plasma cells in the dermis. Usually the spirochete is found only in the epidermis. The predominating involvement of the epidermis in yaws is in contrast to syphilis, in which disease the main changes and the spirochetes are found in the corium. In the scaly macular lesions epithelial proliferation is slight and cellular infiltration is scanty. Late lesions may ulcerate and show epithelial hyperplasia. According to Ferris and Turner,⁸ histologic differentiation of the cutaneous and subcutaneous lesions of yaws and syphilis is unreliable.

Yaws differs from syphilis in that (1) the initial lesion is extragenital, (2) the infection is acquired most often in

childhood but is never congenital, (3) there is absence of mucous membrane lesions in the secondary stage, and (4) macular eruptions (roseola), iritis, and alopecia are uncommon. A long latent period between secondary and late manifestations is unusual in yaws, but the tertiary lesions are similar to those of late syphilis. Skeletal involvement is common with a high incidence of osteoporosis. Yaws is a milder disease than syphilis, and there is a less frequent involvement of cardiovascular and nervous systems. Gangosa (a destructive nasopharyngitis), goundou (an exostosis of nasal bones), and juxta-articular nodes have been considered sequelae of yaws.¹⁰



Fig. 44.—Pinta. (From Sutton and Sutton: Diseases of the Skin, courtesy Dr. Howard Fox.)

Pinta (Carate, Mal del Pinto).—Pinta is a noubenereal infection due to a spirochete, *Treponema carateum* (*Treponema herrejoni*), morphologically indistinguishable from the spirochete of syphilis. It is common among dark-skinned peoples of Central and South America, and particularly in Mexico

and Colombia. The exact method of transmission is undetermined, but probably it is by direct contact. Insect transmission also has been suggested. The Wassermann and Kahn reactions are positive in most cases, and arsenicals are effective in therapy. An eosinophilia (10 to 70 per cent) occurs in 75 per cent of cases.

The initial lesion is a persistent nonulcerating papule, followed in five or more months by secondary lesions (pintids) in the form of macules and papules. The tertiary stage is marked by pigmented spots, most characteristically of a slaty-blue color. The terminal stage is a disfiguring white area of complete depigmentation. The lesions tend to be symmetrically arranged, and usually are on the extremities. Except in the terminal stage, spirochetes are demonstrable in lymph extracted from the lesions by dark-field examination, and in the epidermis by silver impregnation of histologic sections.

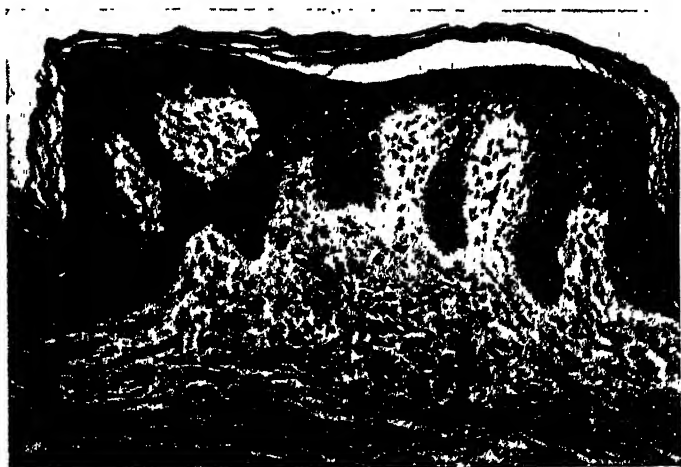


Fig. 45.—Pinta. Microscopic lesion of skin before the final stage, showing epidermal thickening, absence of basal pigment, melanophores, and inflammatory cells in the corium. (From Sutton and Sutton: *Diseases of the Skin*, courtesy Dr. Howard Fox.)

The earlier lesions of the skin show a thickened epidermis with elongated papillary processes, edema, infiltration of lymphocytes, and scanty basal pigment. The corium shows an abundant perivascular leucocytic infiltration, mainly plasma cells and lymphocytes, and numerous melanophores. The late lesions are characterized by epidermal atrophy with

absence of basal pigment, with many melanophores and lymphocytic accumulation in the corium. The final stage is one of epidermal atrophy with loss of papillae, complete absence of pigment, and fibrosis of the corium. There are lymph nodal lesions similar to those of syphilis, but with the constant presence of melanin pigment. Aortitis and cerebrospinal fluid changes similar to those of syphilis have been described clinically.

Weil's Disease (Spirochetosis Icterohemorrhagica).—Weil's disease (spirochetel jaundice) is a severe prostrating infection, due to a spirochete, *Leptospira icterohemorrhagiae*, and characterized by sudden onset, fever, jaundice, hemorrhagic tendencies, muscular pain, and renal injuries. Spread occurs to man from rats. The organism is excreted in the rat's urine, and human infection occurs through the skin. The condition occurs mainly in crowded communities living under damp, unhygienic conditions, as in trenches during war. Laboratory diagnosis is most easily made by inoculation of blood into guinea pigs. Generalized jaundice is usually but not invariably present.

Damage to capillaries is shown by widely distributed minute hemorrhages. The liver is slightly enlarged and bile stained. Microscopically, one sees biliary stasis in central portions of the lobule, and proliferation of hepatic cells. Focal necrosis may be present. The kidneys exhibit degeneration and necrosis in convoluted tubules and interstitial lymphocytic infiltration. Degenerative changes are common in muscle fibers, particularly those of the calf or pectoral region.

Fusospirochetosis.—A symbiotic infection due to a spirochete, *Borrelia vincentii*, and a long fusiform bacillus, *B. fusiformis* is often referred to as Vincent's infection. The mouth is most commonly affected (trench mouth), with the production of necrotizing lesions, particularly on the pharyngeal or tonsillar areas, or gums. The same organisms are often associated with gangrenous bronchial and pulmonary lesions, and may be found in lung abscesses, probably as secondary invaders. Venereal fusospirochetel lesions also occur, particularly in colored males. The genitalia and perineum are involved by ulcerative and destructive lesions which give rise to intense local pain and foul discharge.¹⁸

Relapsing Fever.—Relapsing fever is a widespread acute spirochetel disease, characterized by recurring paroxysmal attacks of fever and prostration, and disseminated by lice and ticks. The louse-borne type, due to *Borrelia recurrentis*, is

spread in epidemic fashion from man to man by *Pediculus humanus*. Usually there are 1 to 3 febrile relapses, each lasting four to six days. Spirochetes are numerous in the peripheral blood. The mortality is low in otherwise healthy individuals, but has reached 50 per cent in epidemics during periods of famine. The tick-borne form of relapsing fever is epizootic among rats and other rodents, and the causative spirochete, *Borrelia duttoni*, may be transmitted incidentally to man by the bite of a tick of the genus *Ornithodoros*. There are usually 4 or more febrile relapses, lasting two to four days. Few spirochetes are demonstrable in the peripheral blood, and the mortality is very low.

There are no very characteristic pathologic changes. The spleen shows zones around the Malpighian bodies of hemorrhagic congestion and infiltration of neutrophilic leucocytes and mononuclear cells. Spirochetes are abundant and easily demonstrated by silver stains. The liver, kidneys, and heart show mild nonspecific degenerative changes.

Ratbite Fever (Sodoku).—Ratbite fever is usually the result of a bite by a wild rat in which the organism, *Spirillum minus*, is commonly parasitic. Dogs, cats, and mice have also been reported to transmit the infection. A primary lesion develops at the portal of entry, followed by recurring attacks of chills and fever, a cutaneous eruption, lymph node enlargement, leucocytosis, muscular pains, and prostration. The organism may sometimes be demonstrated in blood smears, but it is more commonly isolated from blood by inoculation of mice. Wassermann tests may be positive. The condition responds to treatment with arsenicals. A clinically similar condition which also may follow a rat bite is due to *Streptobacillus moniliformis* (Haverhill fever).²⁰

NONSPIROCHETAL VENEREAL DISEASES

Chancroid (soft chancre).—Chancroidal infection, due to *Hemophilus ducreyi*, is an acute venereal disease characterized by soft genital ulcers, which often are followed by enlargement and suppuration of inguinal lymph nodes. Microscopically, the primary ulcer shows superficial necrosis with many polymorphonuclear leucocytes, fringed by a zone rich in plasma cells and monocytes. Small vessels show marked endothelial swelling.

Gonorrhea.—See pages 70 and 579.

Granuloma Inguinale.—Granuloma inguinale (granuloma venereum) is a chronic specific granulomatous infection involving skin and subcutaneous tissues of external genitalia

TABLE VII
DIFFERENTIAL FEATURE OF CHANCER, SOFT CHANCER, LYMPHOGRANULOMA VENEREUM AND GRANULOMA INGUINALE

	ETIOLOGY	DIAGNOSTIC TESTS	INGUINAL NODES	GROSS FEATURES	MICROSCOPIC PATHOLOGY
Chancere	Syphilis <i>Treponema pallidum</i>	Demonstration of spirochete Wassermann, Kahn, etc. + 1-2 weeks after appearance of chancre	Slight enlargement, discrete, shotty	Hard, painless ulcer	Not pathognomonic; certain diagnosis depends on demonstration of spirochete
Soft chancre chancroid	<i>H. ducreyi</i>	Intradermal test + after 3rd week	Large, suppurative	Soft, ulcerative lesion, often multiple	Not pathognomonic; capillary endothelial swelling a marked feature
Lympho-granuloma venereum	Virus	Frei test	Large, focal necrosis appears after primary lesion has subsided	Primary is small, painless, nonindurated, papular. Later there may be elephantiasis and secondary ulceration; rectal stricture (in females)	Lymph nodes show multiple stellate abscesses surrounded by mononuclear cells
Granuloma inguinale	Donovan bodies, bacillus	Demonstration of Donovan bodies in smear or tissue section	Ulceration may involve inguinal region	Irregular spreading areas of ulceration	Specific large mononuclear cell, with intracytoplasmic clear spaces and Donovan bodies

and inguinal region. The spread is probably by venereal means. Small intracellular structures, called Donovan bodies, are present in the lesions and apparently represent the causative agent. They have been cultivated in the yolk of developing chick embryos.²² The lesions show luxuriant granulation tissue, massively infiltrated by plasma cells, with but few lymphocytes and polymorphonuclear leucocytes. The pathognomonic cell in the lesion is a large mononuclear cell, 25 to 90 microns in diameter, with many intracytoplasmic clear areas filled with the deeply staining round or rod-like Donovan bodies.^{21, 22} These bodies stain intensely with silver salts, giving a closed safety-pin appearance because of ovoid shape and intense bipolar staining.

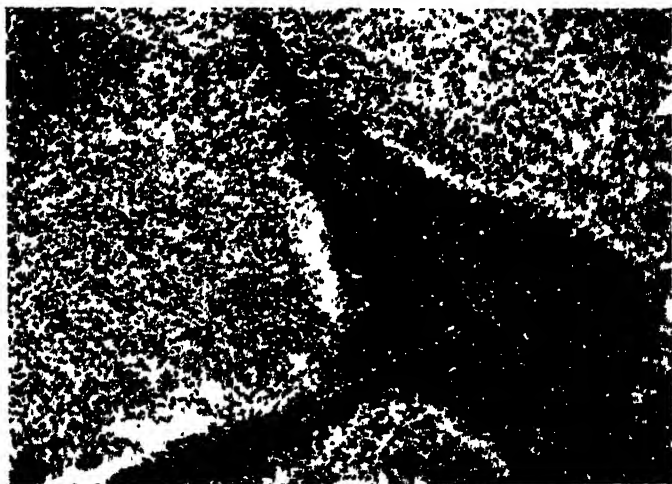


Fig. 46.—Lymphogranuloma inguinale. Characteristic stellate abscess in lymph node. The irregular central cavity containing neutrophilic leucocytes is surrounded by mononuclear cells.

Lymphogranuloma Venereum.—Lymphogranuloma venereum (lymphogranuloma inguinale, lymphopathia venereum) is a virus infection of worldwide distribution, and quite common in America, particularly among the Negro race.²³⁻²⁵ Venereal spread is probably most common. An evanescent and often unnoticed primary lesion is followed later by a variety of manifestations, such as inguinal lymph node enlargement (buboes), genital elephantiasis, rectal stricture, and warty polypoid growths about the anus, vulva, urethra,

and in rectum or vagina. The disease has a marked predilection for lymphatic structures, with resulting lymph stasis, elephantiasis, and ulceration. Constitutional symptoms are common in the acute stage. An immunologic skin test (Frei test) and a complement fixation test are valuable diagnostic aids.²⁸

Lymphatic spread from the primary lesion leads, in males, to the formation of inguinal buboes. In females, lymphatic drainage from deeper parts of vagina and cervix is to pararectal and parasacral glands, and this commonly leads to inflammatory stricture of the rectum. This is the most serious manifestation of lymphogranuloma venereum.

Acute changes in the inguinal lymph nodes are characteristic. Minute miliary abscesses may be evident grossly. Microscopically, there are circumscribed masses of large mononuclear cells, the centers of which become necrotic with the formation of irregular or stellate-shaped abscesses containing many polymorphonuclear leucocytes and surrounded by densely packed mononuclear cells. In the vulvar elephantiasis (esthiomene) the essential change is a thrombotic lymphangitis, with chronic edema and sclerosing fibrosis resulting in induration and enlargement of involved parts. Similar lymphangitis is present in rectal stricture, with the addition of miliary infiltrations of the muscularis by lymphocytes and plasma cells, and ulceration of the mucosa.

On transmission of the virus to mice by the intracranial route, clusters of elementary bodies similar to those of psittacosis may be seen in mononuclear cells composing the exudate in the meninges and in the substance of the brain. The infective agent may be grown in the yolk sac of the chick embryo, smears from which show the elementary bodies.

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CHAPTER VIII

MYCOTIC, PROTOZOAL, AND HELMINTHIC INFECTIONS

MYCOSES

Fungi are cellular filamentous plants belonging to a division called thallophytes. Because of absence of chlorophyll, they must obtain food from organic material already synthesized. They may be saprophytic or parasitic; i.e., they may obtain their food from dead organic material or a living organism. Fungus infections are not rare in man and are frequently serious. Yeasts and fungi may be stained prominently in tissue sections by means of Best's carmine and Bodian activated silver.¹ Superficial involvement of skin or mucous membrane is a common type of fungus infection, as in athlete's foot and thrush. The more serious types of parasitic fungi produce widespread chronic destructive lesions.

Actinomycosis.—Actinomycosis is a chronic suppurative infection due to a streptothrix, the *Actinomyces bovis*. It affects man and certain herbivorous animals, causing "lumpy jaw" in cattle. The organism grows in the tissues in colonies composed of a tangled, felted mass of filaments, surrounded by radiating projections known as "clubs" (hence the term "ray fungus"). Club formation occurs only in tissues, and not in culture, and is thought to be a reaction on the part of the organism to the surrounding tissues. When pus from a lesion is spread in a thin layer on a glass slide, the actinomycotic colonies may be seen grossly as yellow "sulphur granules."

Some break in skin or mucous membrane is apparently necessary to allow entrance of the organism into the body, but the mode of spread of the infection is not known and direct contagion is unproved. The infection is geographically widespread. The region of the mouth, jaws, or face is most commonly affected. The intestinal tract, particularly the ileocecal region and appendix, is next in frequency. Here it may be mistaken clinically for chronic appendicitis, and following operation it may leave a chronic sinus. The liver often becomes involved in any type of abdominal actinomycosis. Oc-

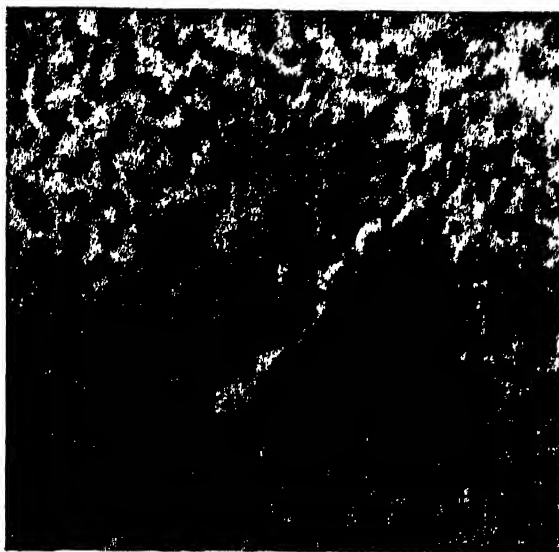


PLATE VI.—Colonies of actinomyces in tissue. Note the radiating structure of the colonies and the peripheral "club" formation. (From Thoma, Kurt H.: Oral Pathology, St. Louis, The C. V. Mosby Company, 1941.)

asionally the Fallopian tubes are infected. Pulmonary actinomycosis may simulate chronic abscess or tuberculosis.

The characteristic lesions are chronic abscesses due to progressive penetration and destruction of tissue. Many leucocytes are present in the zone of suppuration, surrounded by a wall of granulation tissue containing many mononuclear cells and occasional giant cells. In older areas there is marked connective tissue formation. Histologic diagnosis depends on finding the ray fungus in the abscesses.

In the cervicofacial type the lesion usually starts in the gums and spreads to the submaxillary region, where there may be tumor-like masses or soft suppurating lesions, and chronic sinuses from which pus escapes. Occasionally the primary lesion is in the skin. Intestinal involvement produces a chronic inflammatory mass and may lead to suppurating sinuses. Spread to the liver by the portal blood stream, results in multiple, small, ragged abscess cavities. The thoracic type begins in the bronchioles, subsequently involves parenchyma and pleura, with eventual perforation of the chest wall. Spread is rarely through lymphatics, but usually by direct extension or blood stream. Actinomycotic septicemia may result in metastatic abscesses in various organs and tissues.

Mycetoma pedis (Madura foot) is a chronic infection of the foot caused by a variety of fungus-like organisms which may be differentiated by cultural studies. Granules representing colonies of the organism are found in the tissues and in discharged pus. About half the cases are due to actinomyces, and the remainder to a variety of true fungi⁷ (maduromycosis).

Blastomycosis (Gilchrist's Disease).—Infection with *Blastomyces dermatitidis*, a yeast-like organism, most commonly involves the skin, but also may be systemic. The cutaneous type forms a chronic or subacute ulcer which responds to treatment with iodides or radiation. Systemic blastomycosis is highly fatal, with widespread involvement of lung, subcutaneous tissue, nervous system, internal organs, bones, and joints.

Blastomycetes are round or oval unicellular organisms, about 20 microns in diameter, and have a thick refractile double-contoured cell wall. Reproduction takes place in the tissues by budding.

The cutaneous lesions are most frequently on the face, hands, and legs. They begin as papules which slowly ulcerate and extend at the margin. Polymorphonuclear leucocytes accumulate immediately beneath the epidermis, and the sur-

rounding tissue is infiltrated by lymphocytes and polymorphonuclear leucocytes. Giant cells are often present and may contain organisms in their cytoplasm. Certain diagnosis depends on seeing the organisms in the tissue. Pulmonary lesions may have some resemblance to tubercles, but these lesions are differentiated by the presence of pus cells and the blastomycetes.

Rhinosporidiosis.—Rhinosporidiosis is a chronic infection with *Rhinosporidium seeberi*, an endosporulating organism which produces polypoid or pedunculated tumor-like masses on the nasal mucosa. The condition is rare in the United States and is reported most commonly from Ceylon and India.



Fig. 47.—Rhinosporidiosis. Large endosporulating organisms in nasal polypoid structure.

Aspergillosis.—Most members of the genus *Aspergillus* are saprophytic and nonpathogenic. Some are found as harmless invaders of the external auditory canal, the nasal sinuses, and the external genitalia, and as secondary invaders in lung abscesses. In involvement of the ear, the external auditory canal may be partly filled with foul moist material spotted with black granules. Black lesions on the tongue due to aspergillosis also have been reported.

Monilia Infection.—*Monilia* are a group of yeast-like organisms, or *Fungi imperfecti*, of which the chief pathogenic member is *Monilia albicans*, the cause of thrush in children. This lesion is seen in debilitated infants and children as white patches or false membranes on the mucosa of the tongue, gums, lips, cheeks, or pharynx.

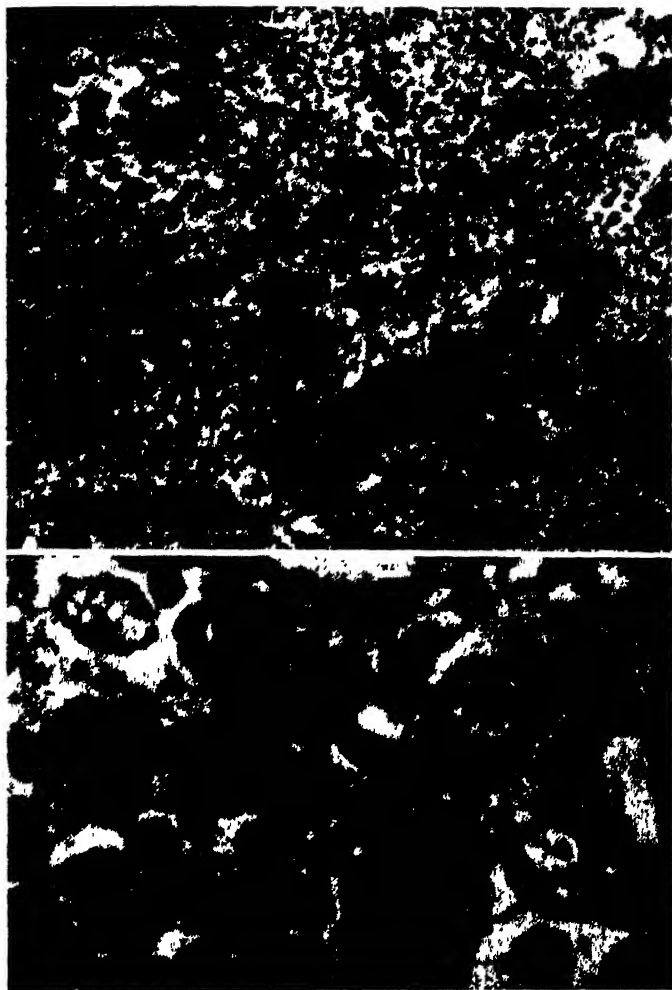


Fig. 48.—Histoplasmosis. Rounded encapsulated organisms in swollen phagocytic cells of the spleen.

Histoplasmosis.—Histoplasmosis of Darling (reticulo-endothelial cytomycosis) is a fatal generalized infection with a yeast, *Histoplasma capsulatum*. The parasites are found in large numbers in phagocytic cells of the reticulo-endothelial system. Originally regarded as a tropical condition, the disease has been recognized with increasing frequency in the United States during the past decade. The highest incidence appears to be in the central area or Mississippi Valley region. The infection has been discovered in a few dogs, but the source of human infections and the portal of entry is unknown. Skin tests with histoplasmin have shown a high incidence of positive reactions in certain states, suggesting that mild infections with *Histoplasma capsulatum* or an immunologically related organism are very prevalent.⁴

Clinically, the condition may resemble primary blood dyscrasias, dysentery, or respiratory infections. Severe anemia and leucopenia with relative lymphocytosis are the usual blood findings. The spleen, liver, and lymph nodes are enlarged. While clinical diagnosis has seldom been made, it is possible by biopsy or by recognition of the organism in mononuclear cells of the blood in blood smears. Infants and children are commonly affected, as well as adults.² Most infected adults have been males.³

The characteristic pathologic change is a widespread reticulo-endothelial hyperplasia, with huge numbers of the encapsulated organisms within the phagocytic cells. Organs most commonly involved are spleen, liver, lymph nodes, lungs, bone marrow, oral mucosa, adrenals, and intestines. Hyperplasia of endothelial cells lining small blood vessels may lead to partial or complete occlusion of their lumens. Ulcerations of the colon, tongue, larynx, and pharynx, and a patchy pneumonitis are also common. Vegetative endocarditis has occurred.

Sporotrichosis.—This uncommon fungus infection occurs mainly in farmers and nurserymen, suggesting that spread may be from plants. The primary lesion is usually on the skin of the arms or hands, but invasion may be by lungs or intestine. The skin lesions are usually multiple, ulcerative, and easily mistaken for gummas. The fungus appears in the involved tissue as a small, spindle-shaped, single-celled Gram-positive organism.

Torula Infection.—Torula is a fungus, variously called *Cryptococcus hominis* and *Torula histolytica*. The parasites are small spheres, measuring up to 12 microns in diameter, and reproduce by budding. The infection most often affects

brain or meninges, but it may also involve lungs, liver, spleen, and kidneys. In the nervous system, the lesions may be meningeal (50 per cent), perivascular, and embolic. The



Fig. 49.—*Torula encephalitis*. Cystic areas in cerebral tissue contain the numerous small round parasites.

meningitis is characterized by pale grayish translucent nodules, easily mistaken for tuberculosis. In about half the cases there are intracerebral lesions. Basal ganglia and midbrain

may be involved as well as cortex. *Torula* usually causes little cellular reaction, but there is a tendency to form tumor-like masses and cysts. Organisms are seen free and within swollen endothelial cells.

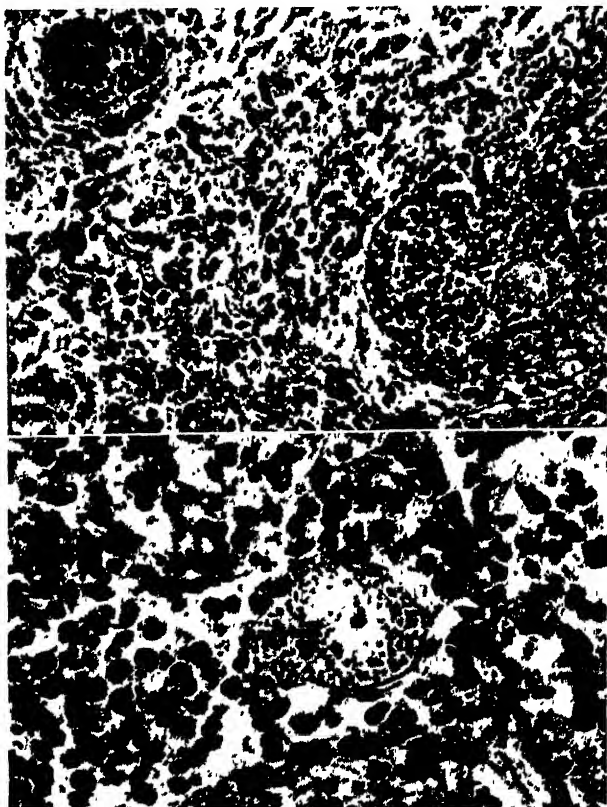


Fig. 50.—Coccidioidomycosis of lung. Note the endospore and multinucleated giant cell.

Coccidioidomycosis and Coccidioidal Granuloma.—Infection with the fungus, *Coccidioides immitis*, is endemic in Southwestern United States, particularly California, but a few cases have been reported in other parts of the Americas. Warm, dry, and dusty areas apparently are suitable for spread of the infective chlamydospores. The portal of entry is the respiratory tract, but in exceptional cases abrasions of

the skin are believed to have been the site of entry of the organisms. In most cases the infection is focalized in the lungs, is self-limited, and asymptomatic. More severe infections may be manifested by an acute respiratory illness ("influenzal" or "pneumonic" form). Sensitivity to the fungus as manifested by skin test with coccidioidin develops ten to forty days after infection, and transient humoral antibodies (precipitins and complement fixation) may be detectable. The allergy as shown by reaction to coccidioidin remains, and the recovered individual is highly resistant to reinfection. A few cases develop manifestations of erythema nodosum or erythema multiforme.

In a small proportion of infections, instead of arrest, there is a progressive or disseminated coccidioidomycosis (coccidioidal granuloma), and in such cases the mortality is high. The lungs, skin, bones, and lymph nodes are most frequently involved. The condition is easily mistaken for tuberculosis or blastomycosis. Diagnostic proof depends on demonstrating the fungus either by culture and animal inoculation, or microscopically in tissue. In tissues the organism may be found free or in giant cells as a rounded body, 5 to 70 microns in diameter, with a highly refractile, double-contoured capsule, and containing endospores. Reproduction by endosporulation differentiates the organisms from blastomyces, which reproduce by budding.

The tissue reactions may simulate those of tuberculosis or of blastomycosis, and differentiation is by recognition of the endosporulating organisms. Abscesses and pseudotubercles develop, with epithelioid cells, multinucleated giant cells, and fibrosis. Pulmonary cavitation may be present.

Chromoblastomycosis.—Relatively uncommon but occurring in widely distributed areas, chromoblastomycosis is an infection by moldlike pigmented fungi belonging to the genera *Hormodendrum* and *Phialophora*. It occurs mainly in farmers or individuals having contact with vegetation, and affects the skin, usually of an extremity, producing a verrucous dermatitis. It does not become systemic. The lesions may be papular, verrucous, or ulcerative. Microscopic diagnosis is made by finding the brown, thick-walled rounded cells of the fungus in the lesion. Epithelial proliferation may be prominent, and a cellular reaction with plasma cells, macrophages, and multinucleated giant cells commonly occurs.

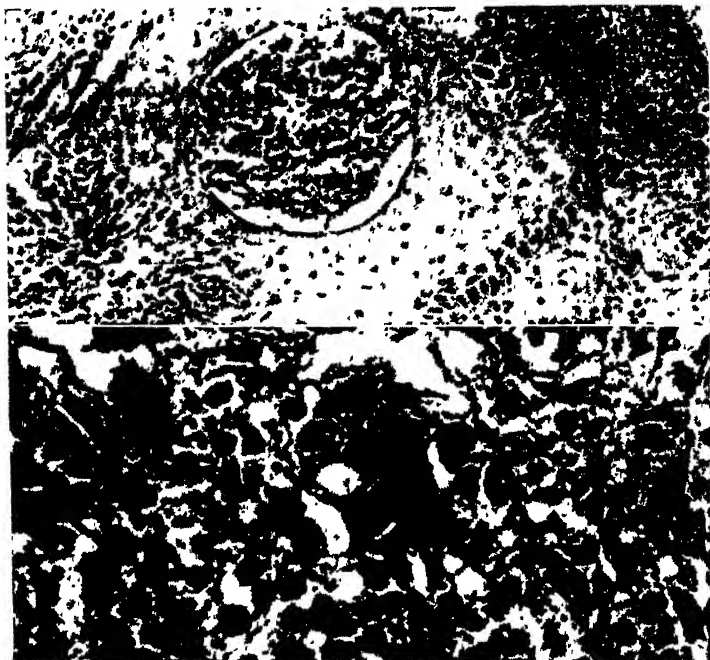


Fig. 51.—Chromoblastomycosis. Note the dark, thick-walled organisms, in a tiny epidermal abscess (top), and budding (bottom).

PROTOZOAL INFECTIONS

The main protozoal diseases in man are amebiasis, due to *Endamoeba histolytica*; malaria, caused by sporozoa of the genus *Plasmodium*, trypanosomiasis, and leishmaniasis.

Amebiasis.—The pathogenic *Endamoeba histolytica* is an actively motile and phagocytic organism, 20 to 30 microns in diameter. It has a single, delicate, barely distinguishable nucleus. It penetrates the tissue of the large intestine, causing characteristic chronic ulcers. Its presence may or may not be associated with the clinical symptoms of amebic dysentery. Metastasis of the amebae through the portal vein to the liver results in hepatitis or liver abscess.

Some of the organisms leave the tissues and become encysted in intestinal contents. The single nucleus undergoes successive divisions to form four small nuclei, and the rounded-up organisms secrete a wall about themselves. Human infection occurs only from ingestion of these cysts. In-

gested cysts develop into four small trophozoites, which penetrate colonic epithelium by their own active movement, aided by a lytic substance which they secrete. Here they produce small areas of gelatinous necrosis or abscesses, which on rupture leave small ulcers. If resistance is sufficient, these lesions may remain small. the infection is symptomless, and the individual is an apparently healthy carrier.



Fig. 52.—Amebic colitis. Note the shaggy and irregular areas of ulceration. (Courtesy Dr. H. C. Schmeisser.)

With inadequate resistance, the amebae penetrate the submucosa and extend laterally, producing large, characteristically undermined and flask-shaped ulcers. The ulcers have shaggy, yellowish-brown edges and a floor formed by submucous or muscular coats. Secondary bacterial infection from the intestine is usual. In severe cases there may be perforation of muscular and serous coats and general peritonitis or adhesions to neighboring structures. The cecum, flexures, and rectum are common sites, but any portion of the large bowel, including the appendix, may be involved. The small intestine is rarely affected. Microscopically, the lesions show an absence of polymorphonuclear leucocytic reaction until secondary infection occurs. Gross diagnosis depends on recognition of the characteristic undermined and flask-shaped lesions, and microscopic diagnosis on recognition of the amebae in the tissues.

Liver abscess is the most frequent complication. It may be single or multiple and have a diameter of a few millimeters or many centimeters. The lining is rough and shaggy, and in older abscesses there is a connective tissue wall. The contents are grumous, semi-fluid, and yellowish red or chocolate colored. Microscopically, the amebae are found in the edge of living tissue and in the adjacent necrotic material. Occasionally, transportation of the organisms by hepatic veins results in a similar lung abscess.



Fig. 53.—Amebic ulcer of colon. Note undermining of edges and characteristic shape. (U. S. Army Medical Museum.)



Fig. 54.—Amebae in submucosa and invading muscularis, amebic colitis. Note absence of any marked tissue reaction. (U. S. Army Medical Museum.)

Balantidium Coli Infections.—See p. 486.

Malaria.—Malaria is an infection with a protozoan parasite which has an asexual cycle in man, and a sexual cycle in the anopheles mosquito. The parasite is a sporozoon, and three common species infect man, causing three types of the disease: *Plasmodium vivax* (tertian malaria), *Plasmodium malariae* (quartan malaria), and *Plasmodium falciparum* (estivo-autumnal or malignant tertian malaria). A rare fourth type is that due to *Plasmodium ovale*. They differ in time required for the completion of a cycle in man, paroxysms of chills occurring at the time of sporulation.

THE PARASITE CYCLE.—The parasite is injected into man by the bite of an infected anopheline mosquito. The parasite invades a red blood cell, where it enlarges and matures, producing a characteristic large form (schizont) which can be identified by appropriate stains of the blood. The intracellular parasite makes use of the hemoglobin in the red cell, using up the protein fraction and leaving the "heme" portion as a brownish granular "malarial" pigment, which is a form of hematin, and not melanin.⁸ By intracellular division the large form breaks up into a number of small forms (merozoites). Rupture of the red cell releases the pigment and merozoites into the blood stream. Each of these attacks a new red cell and the asexual cycle (schizogony) is repeated. The time taken for completion of this cycle is quite uniform and constant for the particular type of parasite. Consequently large numbers mature and rupture into the blood stream at about the same time producing the characteristic malarial chill which recurs at regular intervals.

A few of the intracellular parasites develop sexual forms, called microgametes and macrogametes, instead of the asexual sporozoites. These forms, when released into the blood stream, do not re-enter new red cells, but perish unless taken into the stomach of an anopheline mosquito along with its blood meal. In a mosquito's stomach the micro- and macrogametes fuse to produce a motile fertilized form (zygote), which penetrates the wall of the stomach and forms a cyst (oöcyst). Large numbers of spores develop within this cyst, eventually reach the salivary glands of the mosquito, and are ready to infect the next person bitten.

GENERAL PATHOLOGY.—Pathologic changes in malaria are dependent on the following factors: (1) large numbers of red cells are parasitized and destroyed, with production of a secondary anemia. (2) The malarial pigment (hematin) is a peculiar breakdown product of hemoglobin, and is produced

in large amounts. It does not occur normally in the body and is not an intermediate product in the breakdown of hemoglobin and the formation of bile pigment. By some it is believed to have toxic properties responsible for many of the manifestations of malaria. It seems more likely that its ill effects are produced by promotion of vascular obstruction and thromboses, rather than by any inherent toxicity. The pigment is taken up by phagocytic cells of the reticulo-endothelial system. The resulting reticulo-endothelial hyperplasia contributes to enlargement of the spleen and liver. The deposited pigment imparts a slaty-gray or grayish-black color to the enlarged spleen, and to a lesser extent discolors the liver. (3) Obstruction of small blood vessels is probably the most important factor in the pathology of malaria. This is due mainly to the formation of small agglutinated masses of parasites, red cells, pigment, and fibrin. The presence of the foreign pigment, hematin, may be an important factor in the thrombotic process. The vascular obstructions result in insufficient blood supply to various tissues. In certain organs, e.g., the brain, this ischemia may result in dysfunction or even the development of small areas of necrosis.

LESIONS IN INDIVIDUAL ORGANS.—

Spleen.—The spleen may be greatly enlarged and is discolored a slaty gray or grayish black. Microscopically, an enormous amount of pigment and many parasites are seen in phagocytic cells.

Liver.—The liver is usually only slightly enlarged and discolored. Microscopically, pigment is seen in the Kupffer cells lining the sinusoids. Occasionally, small focal areas of necrosis are present.

Bone Marrow.—In the bone marrow some hyperplasia and retention of pigment are evident microscopically.

Nervous System.—Tiny areas of hemorrhage and focal necrosis with softening may be found in the brain and cord. Cerebral involvement occurs particularly with severe *P. falciparum* infections. Small blood vessels here, as in other tissues, appear congested and obstructed with agglutinated masses of parasitized red cells. In cases not too rapidly fatal the so-called "malarial granuloma" of Dürk may be found. Around a central occluded capillary is an area of necrotic tissue, surrounded in turn by a zone of extravasated red cells and proliferating neuroglial cells. The necrotic material is removed, and a cellular nodule of neuroglial cells remains. The effects of cerebral lesions in malaria depend on their position and extent.⁹

Kidney.—Usually no gross changes are evident in the kidney. Mild microscopic changes occur constantly. These are mainly tubular degenerations and blockage of tubules by casts. In certain cases, as in the complication called "blackwater fever," the renal changes are severe.

Blackwater fever develops in certain cases of malaria. There is an intense hemoglobinuria with the passage of red or reddish-black urine. This complication is usually fatal. The reason for its development in certain cases is unknown. The kidneys show marked degeneration, particularly of the convoluted tubules, and many tubules contain pigment casts blocking their lumens.

Leishmaniasis.—This is a tropical condition, due to protozoan parasites with a complex life cycle. Transmission is by the phlebotomas fly (sandfly). The three main types of *Leishmania* are morphologically indistinguishable.

1. *Leishmania donovani* produces the disease kala-azar (visceral leishmaniasis), prevalent in India. The organism can be seen in phagocytic cells of the reticulo-endothelial system. The intracellular parasites in tissue sections resemble *Histoplasma* but can be differentiated by the presence of the kinetoplast and the lack of a capsule. The spleen is greatly enlarged.

2. *Leishmania tropica*, produces oriental sore (cutaneous leishmaniasis), a chronic granulomatous ulcer, prevalent in the Mediterranean region.

3. *Leishmania braziliensis* (American leishmaniasis, mucocutaneous leishmaniasis) results in chronic granulomatous ulcers, similar to the oriental sore. There is a marked tendency to involvement of the skin and mucosa of the mouth, nose, and pharynx. The ear is also commonly involved, especially among chicle workers of Yucatan (chiclero ulcer). It occurs in Central and South America.

Trypanosomiasis.—Trypanosomes are large, flagellated protozoan parasites, closely related to the *Leishmania*. The African strains, *Trypanosoma gambiense* and *T. rhodesiense*, are spread by the bites of *Glossina* (tsetse) flies, and cause African sleeping sickness. Trypanosomes are found in the blood, and often in cerebrospinal fluid. The lymph nodes are generally enlarged and soft, but most strikingly the nodes of the neck and groin. Chronic meningoencephalitis and meningomyelitis are present, most marked about the pons and medulla. Microscopically, there is a perivascular infiltration of small round cells.

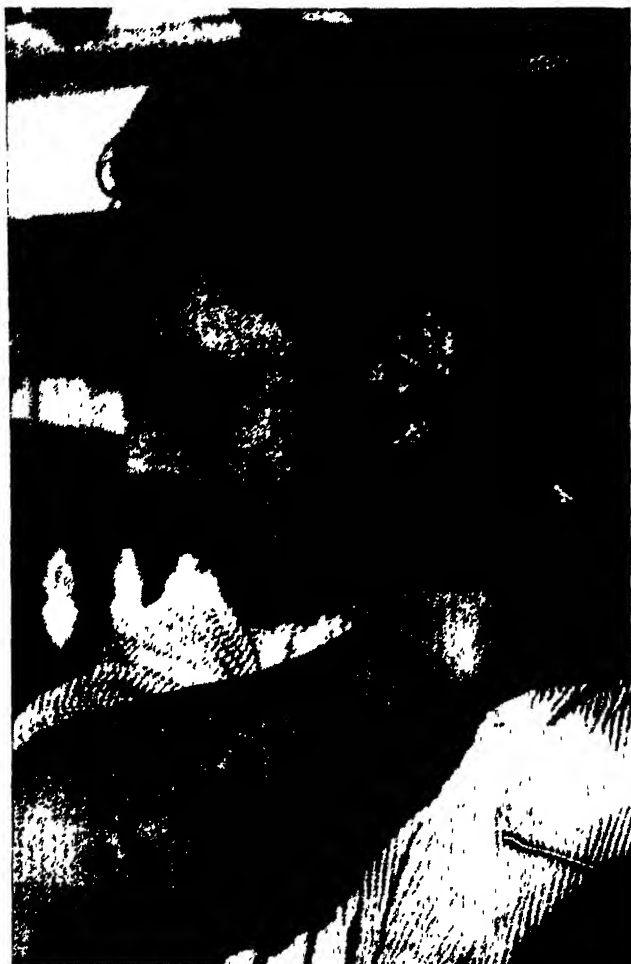


Fig. 55.—American leishmaniasis (Costa Rica). Cutaneous lesions of arm and ear (Chiclero ulcer).

The American type of trypanosomiasis (Chagas' disease), caused by *Trypanosoma cruzi*, is found in various parts of Central and South America. Spread to man is by various triatomid bugs, infective forms passed in the kissing bug's excreta contaminating the bite wound or other abrasions of the skin. Bats, armadillos, rats, and other animals act as reser-

voir hosts. In man or other mammals the trypanosomes leave the blood and enter tissue cells, where they assume leishmania forms. The heart, brain, and liver are most commonly involved, but almost any tissue may be invaded. The heart is enlarged and microscopically shows a diffuse myocarditis and leishmania forms in the muscle fibers. Most acute cases occur in children.

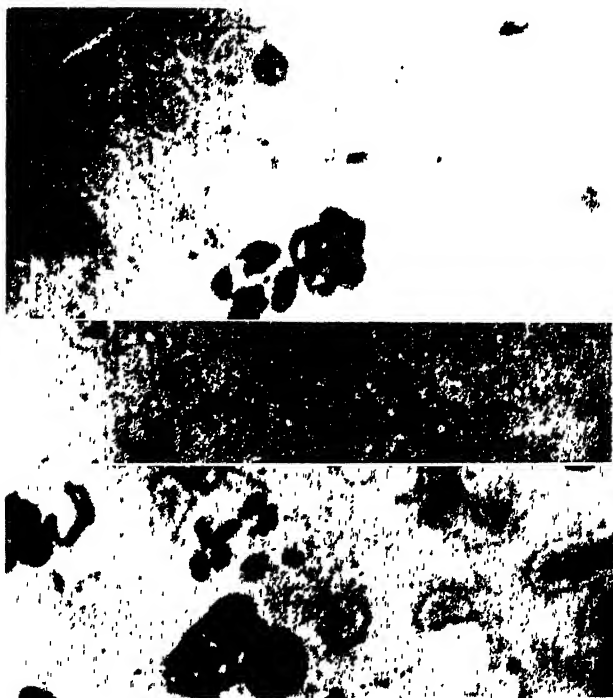


Fig. 56.—American leishmaniasis. Smear from cutaneous lesion (Fig. 55) showing intracytoplasmic and extracellular leishmania, in some of which the nucleus and kinetoplast are distinguishable.

Toxoplasmosis.—Toxoplasmosis is a recently recognized general infection caused by a protozoon, *Toxoplasma*. The congenital form of the disease in infants is an acute or sub-acute granulomatous encephalitis, with hydrocephalus, convulsions, and a characteristic type of bilateral chorioretinitis. Presumptive clinical diagnosis is based on the recognition of this ocular lesion by ophthalmoscopic examination, with evi-

dence of hydrocephalus and focal intracerebral calcification on roentgenologic examination, and on the presence of several hundred lymphocytes and erythrocytes per c. mm. in the spinal fluid.

Since the lesions develop in utero it must be assumed that the mothers of the affected infants, although manifesting no clinical evidence of illness, are latently infected with the organism. The disease occurs in several lower animals, including the dog, but the mode of transmission to man is unknown.

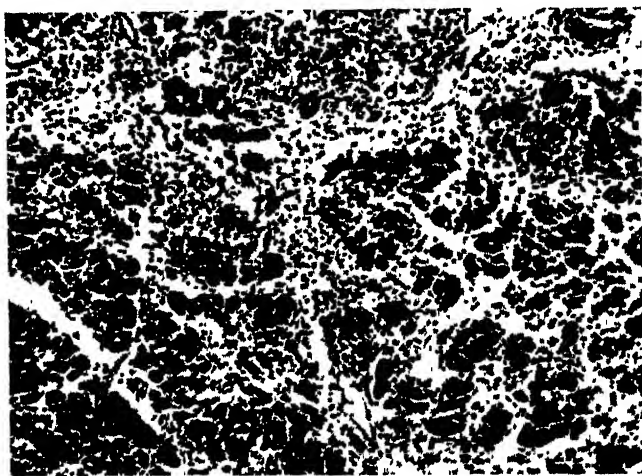


Fig. 57.—Myocarditis in Chagas' disease.

In fatal cases of the congenital type, hydrocephalus is found, with necrotic granulomatous foci in the brain, ranging from microscopic size up to 1 cm. or more in diameter. These lesions are numerous in the walls of the dilated ventricles, and toxoplasma organisms are readily found in them. The myocardial fibers are often distended with large compact clusters of protozoa, and focal lesions with organisms are sometimes present in the liver and elsewhere.

Cases surviving the acute stage of the disease may live on into late childhood with poor vision, mental retardation, persisting hydrocephalus, convulsions, and other manifestations of residual damage to the nervous system. Definite diagnosis during life may be made by finding the organisms

in the spinal fluid, or by transmitting the disease to guinea pigs or mice by the injection of spinal fluid or blood. Immunologic tests for the presence of the infection are being developed.

The rare cases of acute toxoplasmosis in adults have shown interstitial pneumonitis, while cerebral lesions have been scarce and of microscopic size.

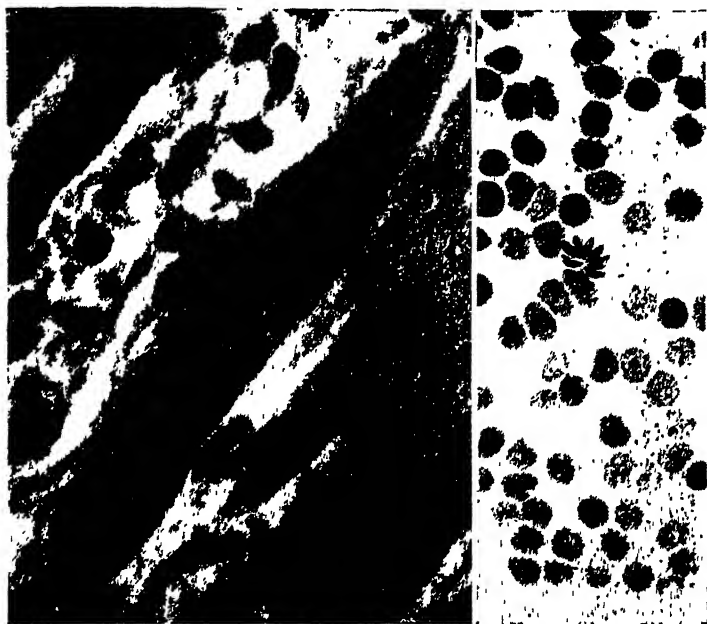


Fig. 58.—Toxoplasmosis. *Toxoplasma* in human heart muscle (left) and in a Giemsa-stained preparation from the omentum of a guinea pig (right). (From Pinkerton, H., and Henderson, R. G.: J. A. M. A. 116: 807, 1941).

WORM INFECTIONS

The three large groups of parasitic worms are the *Nematoda* (roundworms), the *Trematoda* (flukes), and the *Cestoda* (tapeworms). Some worms have developed a complex life cycle, and most of them have an animal host in which they pass a larval phase and are parasites of man during their adult stage. One type, the *Taenia echinococcus*, passes its larval stage in man, and its adult life in the dog.

Roundworms

Ascaris Lumbricoides.—*Ascaris lumbricoides*, the common roundworm, is a long, cylindrical, nonsegmented worm, with separate male and female forms. Its average length is about 20 to 23 cm. Infection is acquired by ingestion of fertilized eggs, which hatch in the duodenum. Here they penetrate lymphatics and are carried to the blood and thence to the lungs. In the lung they penetrate alveoli and are coughed



Fig. 59.—*Oxyuris vermicularis* (pinworms) in the lumen of the appendix.

up in sputum. Some are swallowed with the sputum and develop into mature worms in the small intestine. About two months are required for the complete cycle. The female may produce as many as 200,000 eggs daily. The presence of the worms may cause some slight irritation of the gut, but more often is either symptomless, or causes trouble only by obstruction of appendix, bile ducts, etc.

Enterobius Vermicularis.—*Enterobius vermicularis* (*Oxyuris vermicularis*, pinworm) is a tiny worm 5 to 12 mm. in length. It is especially common in children. Infection results

from ingestion of fertilized eggs, which hatch in the duodenum. Maturation and copulation occur in the small intestine, after which the females migrate to the large bowel, pass out and lay their eggs about the anus. Itching in the anal region is a common symptom. Occasionally, female pinworms in the appendix cause irritation, inflammation, and obstruction, simulating appendicitis (see page 495).

Ankylostoma (Hookworm).—The hookworm, a common parasite in southern areas of the United States, is about 1 cm. in length, and its anterior end is bent to give the appearance of a hook. The mouth has chitinous plates (or teeth) by which the worm attaches itself to the intestinal mucosa.

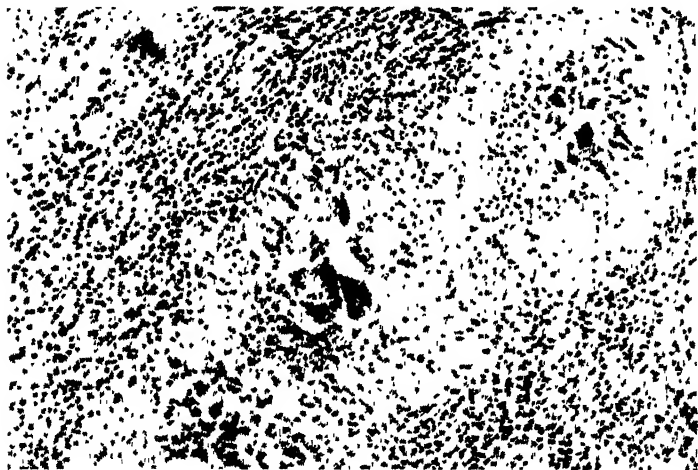


Fig. 60.—*Trichinella bancrofti* infection. Inflammatory reaction in epididymis.

The small intestine, its habitat, may show numerous bleeding spots as a result of injury thus produced. Ova are passed in the feces, and if deposited in warm moist soil, hatch and produce larvae. In about five days the larvae are infectious for man, and are able to penetrate skin with which they come in contact. At the site of penetration, usually between the toes, there is a mild local inflammation (ground itch). The larvae enter subcutaneous venules, pass to the lung, and then by way of trachea and esophagus, to the small bowel. The condition is often accompanied by severe anemia, eosinophilia, and evidence of general intoxication.

Filariasis.—The filariae are roundworms which live in the lymphatics or tissues of man. The most widespread is *Wuchereria bancrofti*, found in parts of Central and South America, Africa, India, Asia, and various Pacific Islands. At one time there was a focus of cases in South Carolina. The adult worms live in the lymphatics of man, mainly in the pelvic region and in the genitalia in the male, causing an obliterative



Fig. 61.—Microfilariae of *Wuchereria bancrofti* (epididymis).

granulomatous lymphangitis. Eventually this may result in lymphatic obstruction and consequent elephantiasis of scrotum or limbs. About a year after infection, larvae (microfilariae) appear in the blood, usually with nocturnal periodicity. The microfilariae when taken up by various culicide and anopheline mosquito vectors develop into infective forms. Infections with *Wuchereria malayi* are similar, although the microfilariae are somewhat different.

Loa loa is a filaria found in central and west Africa, transmitted by a biting fly, Chrysops. The worms migrate in connective tissues, producing transient swellings (Calabar swelling), and may appear in the conjunctiva. The microfilariae appear in the blood in the daytime.

Dracunculus medinensis (Guinea worm) is found mainly in Africa. The threadlike female, as much as a meter in length, lives in subcutaneous tissues. The microfilariae are not found in the body, but are discharged through a blister of the skin on contact with water. The intermediate host is a cyclops, and transmission to man occurs when an infected crustacean is swallowed with water.



Fig. 62.—Onchocercoma; adult worm, containing many microfilariae, embedded in inflammatory nodule.

Onchocerca volvulus is a nematode causative of onchocerciasis. It is found in circumscribed areas of Guatemala and Mexico (at elevations of 1100 to 5000 feet), and in west Africa. Spread is by the gnat or black fly, Simulium. The adult worms are found in localized inflammatory fibrous nodules (onchocercomas), most common in American onchocerciasis in subcutaneous tissue of the head region. Microfilariae are found in superficial parts of the skin, particularly abundant near the nodule, but also at a distance. An erysipeloid dermatitis, eosinophilia, and ocular disturbances are common manifestations. Invasion of the eye by microfilariae frequently produces visual disturbances and blindness.

Trichinosis.—*Trichinella spiralis* has been found to infect 15 per cent or more of individuals examined at autopsy in various parts of the United States.¹⁸ Considering this high incidence, clinical symptoms are uncommon. The infection is common in rats, from which pigs and other flesh-eating mammals become infected. Ingestion of partially cooked or raw pork containing the larvae in muscles frees the encysted larvae in the small bowel. Here they mature and give birth to larvae which invade tissues, penetrate blood vessels, and reach the voluntary muscles, where they become encysted.



Fig. 63.—Encysted trichina in voluntary muscle.

The extraocular muscles, masseters, tongue, larynx, diaphragm, cervical and intercostal muscles are most frequently and heavily involved. Sites of tendinous insertions especially are affected. Occasionally a massive encystment in muscles is accompanied by myositis, with swelling, pain, and tenderness. Muscle fibers degenerate and focal inflammatory reactions occur about the larvae. After a time the encysted larvae die and become calcified. Interstitial myocarditis, with infiltrations of neutrophilic and eosinophilic leucocytes, is common in trichinosis, although the larvae almost never encyst in the muscle of the heart. Inflammatory and hemorrhagic foci may be found also in the central nervous system. Clinical trichinosis may have allergic manifestations.¹⁹

Flukes

The trematodes or flukes are nonsegmented flatworms which live in the blood or tissues, and have complicated life cycles. Those most important in man are the blood flukes (schistosomes), the liver flukes (*Clonorchis sinensis* and *Fasciola hepatica*), and the lung fluke (*Paragonimus westermani*).

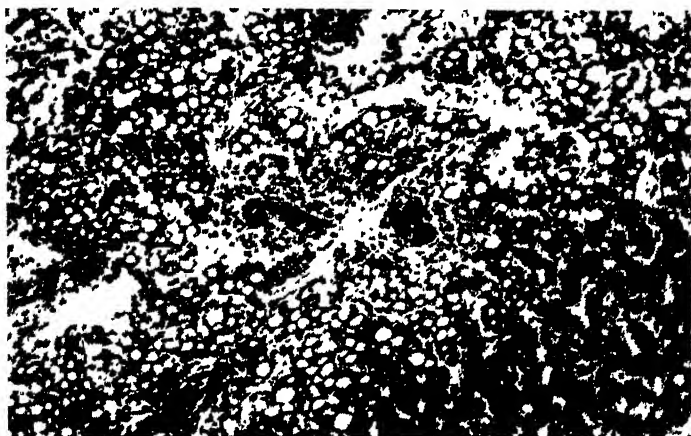


Fig. 64.—Liver, *Schistosoma mansoni*. Two irregular remnants of ova are seen in the center.

Schistosomiasis.—The male and female blood flukes live in various parts of the portal blood stream, the eggs being excreted with feces or urine. The eggs hatch in water, and the resulting free-swimming organisms (miracidia) attack and infect appropriate species of snails. After a period of development and multiplication in the molluscan host, fork-tailed free-swimming forms (cercaria) are discharged, and can penetrate human skin coming into contact with the infected water. Transient local irritation or an urticarial rash may appear at the site of entry in the skin. Penetrating peripheral venules, the larvae are carried in the blood stream and those which reach the portal circulation survive and mature. The important lesions which develop are due to the deposition of eggs in the liver, walls of bowel and bladder, and other tissues.

Schistosoma haematobium (Bilharzia) is most prevalent in northern Africa. The pelvic veins, particularly the vesiculo-

prostatic plexus, are the frequent location of the parasites, the terminal-spined ova being deposited in the wall of the bladder and passed in the urine. The irritation of the ova in the bladder wall gives rise to cystitis, hematuria, and sometimes carcinoma of the bladder. The rectal wall also may be affected.



Fig. 65.—Appendix, schistosomiasis due to *Schistosoma japonicum*. Note ova in muscularis and submucosa, and tubercle-like lesion.

Schistosoma mansoni infections are widely distributed in Africa, northern South America, and the Caribbean region. The mature worms locate mainly in the lower colonic and

rectal branches of the portal veins. The lateral-spined eggs extruded into the intestinal wall cause a chronic inflammatory reaction. Pseudotubercles and small abscesses form around the ova, and fibrosis and thickening of the bowel wall eventually develop. Many ova are carried by the portal stream to the liver and deposited around portal spaces, where they cause formation of pseudotubercles and fibrous nodules. Eventually, this may lead to a progressive portal cirrhosis, with obstruction of the portal circulation, splenomegaly and ascites (see p. 390).

Schistosoma japonicum infections are common in the Far East, particularly in the Yangtse Valley of China, and areas of Japan, Formosa, and the southern Philippines. The adult worms are most commonly in branches of the superior mesenteric vein draining the small intestine. The eggs, which have but a small rudimentary lateral spine, are extruded through the wall of the small bowel, where they cause much irritation, dysenteric symptoms, chronic inflammation and fibrous thickening. Many eggs are carried to the liver, where they cause pseudotubercle formation, periportal fibrosis, portal obstruction, splenomegaly, and ascites.

Nonhuman varieties of schistosome cercariae have caused severe dermatitis (swimmer's itch) in some areas of the United States, although the parasites are incapable of developing to maturity in man.

Tapeworms

Tapeworms are long, segmented, hermaphroditic worms, having a small head provided with suckers and hooklets. Each mature segment may produce a large number of eggs. With the exception of the dog tapeworm (*echinococcus*) and sometimes the pork tapeworm (*cysticercosis*), man harbors the mature worm, and larval forms occur in an intermediate host.

Hymenolepis Nana (Dwarf Tapeworm).—*Hymenolepis nana* is the smallest human tapeworm, and the commonest in the United States. The adults are 10 to 40 mm. long, and may be numerous in the upper ileum. Infection is usually acquired from rodents.

Taenia Saginata (Beef Tapeworm).—Living encysted embryos of *Taenia saginata* are ingested with insufficiently cooked beef. It is the second most common tapeworm in the United States. The adult worm has a small pyriform head with four lateral suckers, and a body with one to two thousand segments, extending for many feet. Symptoms may be slight

and are due to irritations from their large size, and absorption of food from the intestine.

Taenia solium (Pork Tapeworm).—In *Taenia solium* infection the intermediate host is the hog. The worm is 8 to 12 feet long, has a small globular head with four sucking discs and a number of hooklets, and about 1,000 body segments. While uncommon in the United States, the pork tapeworm is particularly important because the larvae as well as the adult can develop in man. Hence when infection is present, precautions to prevent ingestion of eggs are essential. If eggs are ingested by man, embryos liberated by action of gastric juice migrate into the body tissues and become encysted (cysticercosis). The brain, eye, muscles, heart, liver, and lungs have been involved by the larval cysts, with disturbances due to the space which they occupy and the surrounding inflammatory reaction.²⁴

Diphyllobothrium Latum (Fish Tapeworm).—*Diphyllobothrium latum* undergoes two stages intermediate between man, a larval stage in a cyclops and an encysted stage in fresh water fish. The adult worm is long and has an almond-shaped head with two lateral sucking grooves, but no hooklets.

Taenia Echinococcus (Dog Tapeworm).—In the case of *Taenia echinococcus*, the adult worm is found in the dog, and the intermediate larval form occurs in cattle, sheep, hogs, man, and other mammals. Dogs acquire the infection from eating carcasses of sheep, cattle, and hogs in endemic areas. The adult worm is small, measuring 3 to 5 mm. in length. The head is distinctive, with four sucking discs and a circle of hooklets. Three segments constitute the body. The ova passed with dog's excreta, are usually ingested by man with uncooked vegetables. Larvae develop in the intestine, penetrate the wall into blood vessels, and pass to the liver and other organs. Lodged in an organ they form cystic structures, known as hydatid cysts, which vary up to 20 cm. or even more in diameter. The cysts have a white outer layer and a granular inner germinal layer. From this inner layer, new cysts develop, and scoleces, or heads, of new worms are formed. These can be recognized by seeing the row of hooklets. Eventually the larvae die out, and the cyst becomes converted into a putty-like mass with calcification of the capsule. Material from hydatid cysts, used as antigen, results in a skin reaction which may be helpful in clinical diagnosis. Hydatid disease is not commonly acquired in North America, but has a high incidence in Australia, New Zealand, Uruguay, Argentina, Iceland, and in parts of Europe.

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CHAPTER IX

CHEMICAL POISONS

Poisons are chemical agents which injure tissues by their reaction with them. With many poisons, the effects depend on the quantitative factor of dosage, and many substances which are innocuous or even necessary to the body in small doses, are harmful when concentrated or in large quantities. While poisoning is an ever popular method of suicide and homicide, many chronic poisonings are the result of industrial hazards (e.g., lead poisoning and silicosis) and as such form an important group of diseases. Some bacterial toxins are very powerful poisons (e.g., tetanus and botulinus toxins). Other types of organic poisons are those of snake-bite and mushroom poisoning.

When poisoning is suspected at an autopsy, the stomach and its content, portions of small and large intestine, and part of the liver and kidneys should be preserved in chemically clean, wide-mouthed, glass bottles with glass tops. These should be sealed by wax with some special imprint or seal and submitted to a toxicologist.

Corrosive Poisons.—The chief effect of corrosive strong acids and alkalis is local destruction of tissues. Sulfuric, nitric, and hydrochloric acids produce rapid destructive effects on mucous membranes when ingested. Similar effects may be produced by contact with the skin. Corrosive action is often evident on the mucosa of the lips, mouth, and pharynx as well as esophagus and stomach. The lesions are reddish brown or black from sulfuric acid, grayish white from hydrochloric acid, and yellowish brown from nitric acid. In the stomach and intestine the crests of mucosal folds are most severely affected. With sulfuric acid the stomach may be intensely red or have a black tarry appearance (carbonization). The stomach wall feels hardened, rough, and dry. With nitric acid there is no hardening, but extensive ulceration and sloughing of the mucosa occur. With hydrochloric acid the tissue is reddened or blackened and shrivelled. The strong acids acting on blood form acid hematin, with widespread brownish-black discoloration.

Ingestion of a corrosive alkali, such as lye, produces softening, swelling, and often ulceration of the mouth, esophagus, and stomach. The stomach feels soapy. If the poisoning is

not fatal, healing occurs with marked fibrosis, severe stricture of the esophagus being a common result.

Phenol (carbolic acid) produces fixation and partial detachment of mucosa. These areas are whitish and of leathery consistence. The characteristic odor of phenol aids in identification.

Mercury.—Corrosive sublimate (bichloride of mercury) has effects which depend on dosage and length of survival

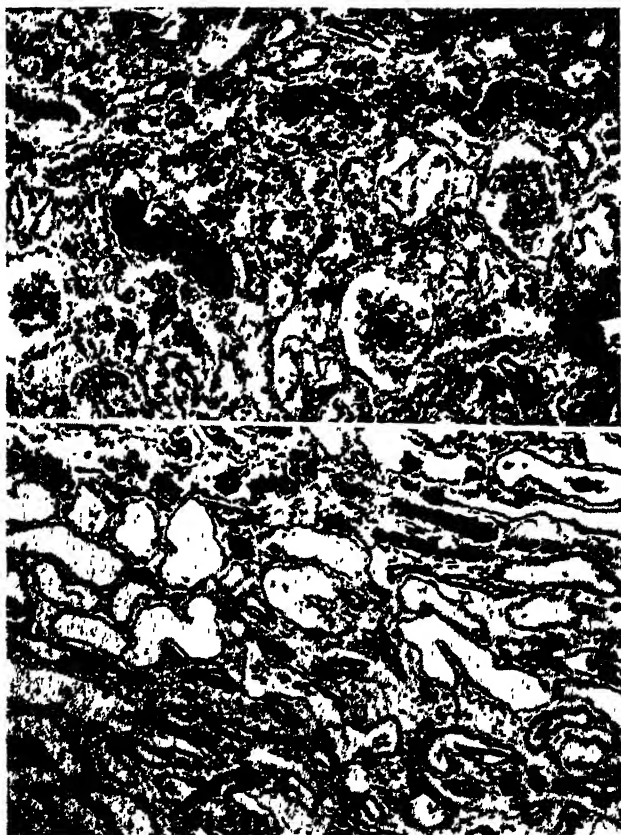


Fig. 66.—Kidney, mercury bichloride poisoning. Upper: Kidney seven days after ingestion of poison. Note destruction and desquamation of tubular epithelium. Lower: Kidney on the eleventh day. Note loss of tubular epithelium, flattened tubular lining, and dark calcium masses in tubular lumina.

time. In the acute cases there is corrosion of the stomach and duodenum, the mucosa of which appears white and opaque. In the colon there is an intense hemorrhagic and membranous inflammation. If there is survival for a few days or weeks, severe destruction of renal tubular epithelium occurs with calcium deposition in the necrotic tubules. In such cases death usually results from anuria. Schenken and Hansmann have pointed out that mercury poisoning may result in a primary severe vascular injury in limited portions of the intestinal tract.¹

Cyanides.—Hydrocyanic acid and cyanides cause very rapid death without leaving diagnostic morphologic changes. The characteristic odor of peach kernel or bitter almonds assists in detecting the poison.

Alcohol.—Methyl alcohol (wood alcohol or methanol) causes poisoning by oxidation to formic acid, injuring particularly the highly specialized tissues of the retina, brain, liver, and kidneys. If there is recovery from acute poisoning, blindness may follow due to atrophy of optic nerves. Repeated ingestion of small quantities of methyl alcohol in denatured alcohol apparently causes no permanent injury.²

Alcoholism due to ethyl alcohol may be of either acute or chronic form. In acute alcoholism death is frequently due to some complication of the intoxication, such as trauma or suffocation, rather than the result of alcoholism itself. The stomach has a hyperemic mucosa, with small petechial hemorrhages or erosions. The brain is wet and edematous, the cerebrospinal fluid appearing to be in excess. **Chronic alcoholism** is associated with several pathologic changes, though few are specific effects of the alcohol per se. The gastric mucosa is involved by a mild chronic catarrhal inflammation. One of the most constant findings is enlargement and marked fatty infiltration of the liver. Portal cirrhosis of the liver is present in 5 to 8 per cent of alcoholic addicts, and 50 to 60 per cent of patients with cirrhosis have a history of alcoholism.³ It seems certain that chronic alcoholism is a factor in many cases of cirrhosis, although the relationship is not a direct one (see p. 388). Many alcoholics suffer nutritional deficiencies, a possible factor in hepatic changes and in another common complication, peripheral neuritis. Resistance to infection appears to be lowered.

Carbon Monoxide.—Carbon monoxide poisoning is due to inhalation of illuminating gas, exhaust of automobiles, or gas from a defective stove or heater. The carbon monoxide

has a much greater affinity for hemoglobin than has oxygen, so that death is due to asphyxia. The blood and congested tissues have an unusually bright-red color. Fatal cases may show symmetric areas of softening or small hemorrhages of the brain, often involving lenticular nuclei or globus pallidus.

Phosphorus.—Acute phosphorus poisoning causes fatty degeneration and necrosis in the liver, and milder fatty changes in heart and kidney. Chronic phosphorus poisoning produces necrosis of the jaws, particularly around infected teeth.

Lead.—Acute lead poisoning is rare, but chronic lead poisoning (plumbism) appears commonly as an industrial disease where lead or compounds of lead are used. Poisoning also may occur from drinking water carried in lead pipes, and from battery casings burned as fuel. Characteristics of lead poisoning are intestinal colic, weakness of extensor muscles, secondary anemia with reticulocytes, polychromasia and basophilic stippling prominent in the blood smears, a blue line on the gums, and mental disturbances. Lead becomes deposited chiefly in bones as a lead phosphate, apparently by a mechanism similar to that causing calcium deposition. Parathyroid hormone will mobilize the lead from the bones. Lead can also be demonstrated in the brain, liver, and kidneys.

The most constant lesions due to lead are the blue line of the gums, and the anemia with stippling of red cells. Other findings frequently present are degenerations of anterior horn cells, a chronic muscular atrophy and fibrosis, degeneration of male gonads, and blue patches on the mucosa of intestine.⁴

Sulfonamide Compounds.—Administration of sulfonamide drugs is complicated in some cases by deleterious effects on many organs, but most serious are the injuries to the kidney and blood-forming tissues. All the sulfonamides have caused damage, but serious effects seem most frequently to follow the use of sulfathiazole. The sulfonamides act as mild irritants and foreign bodies when precipitated in tissues or placed in serous cavities. Many of the more serious reactions to the sulfonamides give evidence of being of allergic nature, particularly the skin rashes and the effects on blood vessels, myocardium and hemopoietic tissues.^{8, 10}

In the urinary tract there occurs the additional complication of obstruction due to precipitation of acetylated derivatives of the sulfonamides in the renal tubules, ureters, and bladder.

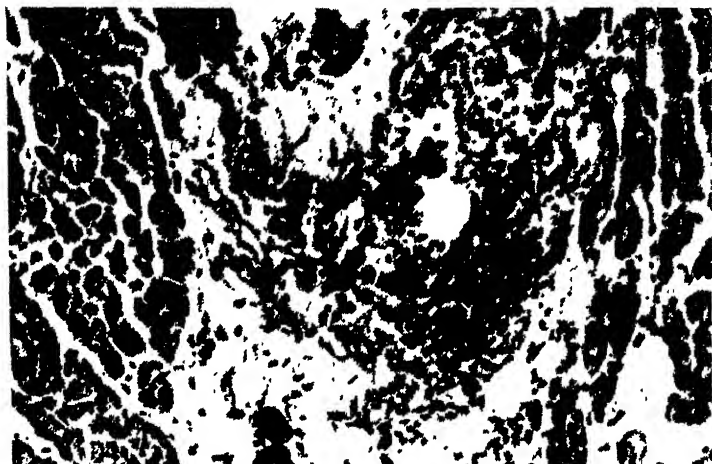


Fig. 67.—Myocarditis in sulfonamide poisoning.

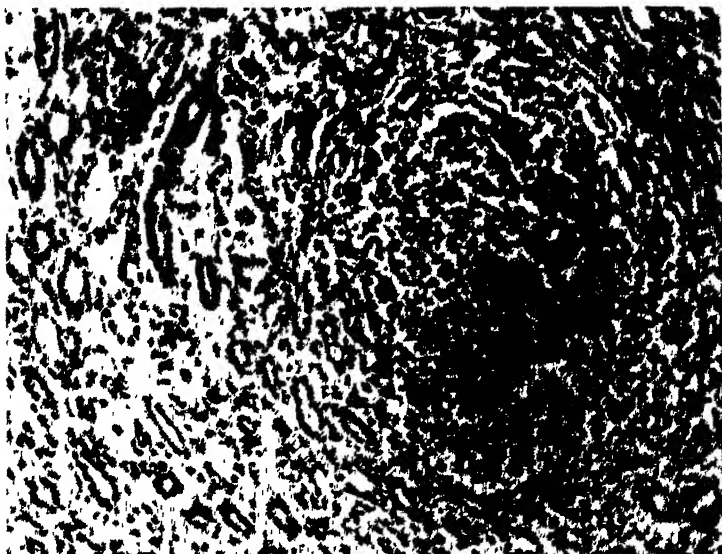


Fig. 68.—Sulfonamide poisoning; focal necrotic lesion of kidney.

In the heart, an interstitial myocarditis in which eosinophiles may form a prominent feature is a common finding.⁷ Blood vessels may show inflammatory changes similar to those of periarteritis nodosa.⁸ Focal necroses may develop in the liver, kidneys, spleen, lymph nodes, adrenals, and other organs.⁵ In the kidneys there may be degeneration and necrosis of tubular lining cells, and tubular obstructions due to precipitated material in the lumens.⁶ Interstitial pneumonitis may be found in the lungs.⁹ Acute anemia and agranulocytosis are associated with bone marrow changes.

Fluorine.—Chronic fluoride intoxication occurs among certain cryolite workers, and in mild degree in areas where drinking water contains more than one part per million of fluorides. Such content in water is found in many parts of the United States, but especially in Southern and Western areas. The earliest and main effect of this is a hypoplasia of the enamel of the teeth called mottled enamel. The permanent teeth are affected during their process of calcification, i.e., during the first 8 or 9 years of life. The fluorine has a direct local action on enamel-forming cells. The teeth show grayish white blotchy or chalky areas on their surfaces, with some irregular pitting. It has been estimated that a daily intake of 0.1 to 0.15 mg. of fluorine per kg. of body weight is sufficient to produce mottled enamel. There is evidence that in geographic areas where mottled enamel is common the incidence of dental caries is decreased. Fluorine appears to have a definite action in protection of teeth from caries, though the mechanism of this is not established.¹¹ Fluorides in larger dosage cause a diffuse osteosclerosis of bones. Such changes have been described in cryolite workers.^{12, 13, 14}

Food Poisoning.—While poisons such as arsenic are sometimes added to food by accident or design, food poisoning usually refers to the effects of pathogenic bacteria growing in the food, or to poisons in plant tissues such as in certain mushrooms. A number of infections by bacteria and worms may be spread by food, but food poisonings with acute gastrointestinal symptoms are mainly due to infection of the food with organisms of the paratyphoid "B" (*Salmonella*) group. Local superficial inflammatory lesions develop in the intestine. Botulism is the toxemia resulting from the ingestion with food of the exotoxin of *B. botulinus*, and its principal effects are on the nervous system. Proper cooking of food will destroy the toxin.

Mushroom poisoning is due most commonly to *Amanita phalloides*, ingestion of which causes acute gastrointestinal symptoms and a high mortality (45 to 70 per cent). Fatty degeneration in the liver, heart, kidneys, and voluntary muscles is the most prominent autopsy finding. Some gastroenteritis may be present and also degenerative changes in the brain.

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CHAPTER X

VITAMIN DEFICIENCIES

Adequate dietary intake is necessary for maintenance of health. Not only is an adequate caloric content necessary, but certain proteins, minerals, and vitamins are essential. Slight deficiency may be difficult to recognize pathologically as well as clinically. The problem is further complicated by the rarity in man of pure deficiencies, such as may be produced in carefully controlled experimental animals. Inadequate human diets often lack several essentials so that the resulting lesions are a mixture.

Vitamins are organic compounds essential in the diet for normal growth and maintenance of life; they are active in the regulation of metabolism and transformation of energy but do not themselves furnish energy or building material, and they are effective in small amounts. Several vitamins, particularly thiamine, riboflavin, and nicotinic acid are closely concerned with intracellular respiration, providing chemical groupings essential for intracellular oxidations and reductions.

Vitamin A

Vitamin A is a fat-soluble unsaturated alcohol and has as its precursor certain vegetable pigments known as carotenes. Deficiency results in night blindness, dermatosis, and xerophthalmia.

One of the diagnostic features of vitamin A deficiency is subnormal dark adaptation. Vitamin A is an essential constituent of retinal pigments used to register visual stimuli. When deficient, regeneration of visual purple is delayed, so that dark adaptation is poor.

The primary effect of vitamin A deficiency is on epithelium, which undergoes atrophy and replacement by a keratinizing type of epithelium. In man the specific lesions are found in the eyes, conjunctiva, lining epithelium of various organs and ducts, and skin with its appendages. The commonest and earliest appearance of metaplastic squamous epithelium is in trachea and bronchi, and next in the pelvis of the kidney. The eye changes are also a metaplasia of the corneal and conjunctival epithelium, followed by corneal infection. The skin is rough, scaly, and dry due to hyperkeratosis of skin and hair follicle epithelium, and metaplasia of sweat gland epithelium.

TABLE VIII
VITAMIN DEFICIENCIES IN MAN

VITAMIN	OCURRENCE	DISEASE	FUNDAMENTAL NATURE AND LESIONS
A— $C_{40}H_{56}O$ Carotene pigments	Fish liver oils, vegetables, milk, butter, eggs	Xerophthalmia, night blindness, dermatosis	Atrophy of epithelium with squamous metaplasia; hyperkeratosis of skin, deficient regeneration of visual purple
B ₁ — $C_{12}H_{17}N_3OSCl_2$ Thiamine hydrochloride	Yeast, whole grains, eggs, many vegetables, etc.	Beriberi	Hypertrophy and dilatation of right heart; edema; degeneration of peripheral nerves
B ₂ or G— $C_{17}H_{19}N_4O_4$ Riboflavin	Yeast, milk, liver, wheat germ, eggs, cheese, etc.	Important in tissue respiration	"Cheilosis"—fissures of the angles of the mouth
B ₆ —pyridoxine $C_8H_{11}O_3N$	Yeast, wheat germ, rice, bran, etc.	Undetermined	
Pantothenic acid $C_9H_{17}O_5N$	Yeast, wheat germ, rice, bran, etc.	Undetermined	
Nicotinic acid (P-P) $C_6H_5O_2N$	Yeast, liver, wheat germ, milk, etc.	Pellagra	Scaly skin eruptions, cystic colitis, patchy degeneration in the central nervous system
C—Ascorbic acid $C_6H_8O_6$	Oranges, lemons, limes and other fresh fruits and vegetables (potatoes)	Scurvy	Deficiency of intercellular cement substance of connective tissues and vascular endothelium. Hemorrhages, interruption of ossification, and rarefaction of bones.
D ₂ —Calciferol $C_{28}H_{44}O_2$	Fish liver oils, eggs, butter and milk	Rickets	Overgrowth of osteoid tissue and defective calcification of growing bones, due to defective absorption of minerals from intestines
E—Alphatocopherol $C_{56}H_{100}O$	Wheat germ oil, green leafy vegetables	Osteomalacia	Adult form of rickets
K— $C_{39}H_{55}O_2$, 2-methyl-1, 4-naphthoquinone	Alfalfa, spinach, fish meal, soy bean, etc.	Undetermined	Promotes hemorrhagic conditions
		Prothrombin deficiency	

Tooth changes are characteristic in vitamin A deficiency and are particularly well seen in the incisor teeth of rodents. The enamel organ undergoes atrophy and metaplasia. Enameloblasts become replaced by squamous epithelium, enamel formation is suppressed, and deformities of dentine result. Similar changes have been described in human infants with vitamin A deficiency.



Fig. 69.—Hyperkeratosis of hair follicle in vitamin A deficiency. (From Sutton and Sutton: *Diseases of the Skin*, courtesy Dr. Chester N. Frazier.)

Vitamin A can be demonstrated in microscopic sections by fluorescence microscopy.² Ultraviolet light is used, the vitamin A exhibiting a fading greenish fluorescence in the dark field. By this method vitamin A has been found distributed in the lipoids of the epithelial and Kupffer cells of the liver, epithelial cells of adrenal cortex, tubular and Leydig cells of the testicle, granulosa, theca, and stromal cells of the ovary, fat cells, gland cells of the lactating breast, and in kidneys with abnormal glomerular permeability.

Vitamin B Complex

Vitamin B has been found to contain a number of specific factors. The chemical nature of most of them being known, they are more properly designated by their correct chemical

name, rather than referred to as B₁, B₂, etc. The factors in the B complex include thiamine hydrochloride, riboflavin, nicotinic acid, pantothenic acid, pyridoxine hydrochloride, etc. The B complex is found in yeast, whole grain cereals, wheat germ, rice polishings, etc.

Thiamine Hydrochloride (B₁).—Thiamine is a water-soluble vitamin, deficiency of which results in beriberi. The main clinical features are loss of appetite, peripheral neuritis with muscle tenderness and changes in reflexes, tachycardia, cardiac failure, and edema. Thiamine is important in the intracellular metabolism of glucose, the pyrophosphate of thiamine acting as a co-enzyme (with carboxylase) in the breaking down of pyruvic acid.

BERIBERI.—Beriberi occurs in acute and chronic forms. The findings in chronic forms when seen at autopsy are usually complicated by an infection. The more acute and uncomplicated forms are characterized by dilatation and moderate hypertrophy of the right heart, generalized edema, hydrothorax, hydropericardium, and congestion of viscera. Microscopically, the heart shows simply enlargement of the individual muscle fibers. Microscopic nerve lesions are most frequent in nerves supplying the lower extremities; cranial and vagus nerves are also frequently affected. There is vacuolar degeneration of Schwann cells, followed by fragmentation of axis cylinders and myelin sheath degeneration.

Riboflavin (B₂ or G).—Deficiency of riboflavin (ariboflavinosis) is said to produce in man a lesion called "cheilosis," characterized by superficial cracks or fissures at the angles of the mouth. A nasolabial seborrheic skin lesion, glossitis, and circumcorneal congestion also may be present. Riboflavin appears to be important in tissue respiration, for combined with phosphoric acid it unites with specific proteins to form enzymes which act as dehydrogenases.

Pantothenic Acid and Pyridoxine Hydrochloride.—The role of these factors of the B complex in human pathology is still uncertain.

Nicotinic Acid (P-P).—Considerable evidence indicates that deficiency of nicotinic acid is an important factor in pellagra, although probably in most cases multiple deficiencies are present. The exact cause of pellagra is unknown and etiologic views are still divergent.³ Nicotinic acid is an essential component of pyridine-protein intracellular enzyme systems, important in carbohydrate metabolism.

PELLAGRA.—Pellagra is characterized by brown, scaly, patchy skin eruptions, and by soreness of the mouth, redness

of the tongue, indigestion, diarrhea, and nervous disturbances. The skin lesions tend to appear particularly in areas exposed to sunlight.

Pathologic changes are found in the skin, gastrointestinal tract, and nervous system. The skin lesions begin with edema of papillae, dilatation of papillary blood vessels, and degeneration of connective tissue of the superficial part of the corium. This is followed by epidermal hyperplasia and hyperkeratosis with increase in pigment. The lesions are similar to sunburn or x-ray dermatitis. In late stages the epidermis is thin and atrophic and the corium fibrosed. The oral mucosa may be affected in a similar fashion.

The intestinal lesions are more characteristic. The colon is thick-walled, reddish, and may have a patchy pseudomembranous change in the mucosa. The mucosa may be infiltrated by chronic inflammatory cells, but most pathognomonic is a cystic dilatation of the crypts of Lieberkühn.

The nervous lesions appear late and are more prominent in the central nervous system than in peripheral nerves. Patchy degeneration may be present in the cerebrum, and in the spinal cord irregular patches of myelin degeneration most commonly involve posterior columns.

Ascorbic Acid (Vitamin C)

Ascorbic acid is a water-soluble vitamin, deficiency of which leads to scurvy. This vitamin is essential for the production and maintenance of intercellular substances of mesenchymal origin, i.e., collagen of fibrous tissue, the matrices of bone, dentine and cartilage, and the intercellular cement substance of vascular endothelium.⁴ Mesenchymal tissues (fibroblasts, osteoblasts, etc.) grow in the absence of vitamin C, but they cannot produce intercellular substance. Hemorrhages and changes in bones are the prominent features of scurvy. In C-deficient animals, fractured bones cannot be restored to functional integrity. The broken ends are united by fibroblasts, but neither collagen nor osseomucin is produced. There is little evidence that excess of vitamin C promotes healing of wounds or fractures,⁵ but deficiency of vitamin C appears to have serious effects and prevents formation of scars of normal strength.⁶

Ascorbic acid has been found in large amounts in the adrenal gland, particularly the cortex. It is also present in the lens and humors of the eye, the corpus luteum, pituitary, and small intestine. Excretion of excess in the urine may be quantitatively determined by the dichlorophenol indo-

phenol indicator. The ascorbic acid content of the white cell-platelet layer of centrifuged blood is the most significant indicator of the vitamin C status of the body. Scurvy does not occur until this is entirely depleted.⁵

Scurvy.—Human scurvy is more common in children (Barlow's disease) than in adults. The essential features are hemorrhages, changes in bones and teeth, and anemia.

The hemorrhages may be in any organ or tissue and vary from small petechiae to massive hematomas. Any injury or trauma to a tissue predisposes to hemorrhage, which is due to changes in the intercellular substance between capillary endothelial cells. Petechial hemorrhages in the skin are most prominent clinically. In infants, very painful subperiosteal hemorrhage is common.



Fig. 70.—Scurvy, showing gingival swelling and petechiae. (From Mead, S. V.: *Diseases of the Mouth*, The C. V. Mosby Co.)

The skeletal lesions are most prominent at the costochondral junctions, the ends of the femurs and tibias, and at the wrists. Grossly there is a curved, yellowish, widened zone at the junction of the diaphysis and cartilage. Microscopically, this zone shows evidence of disordered growth and interruption of the process of ossification. Fragile connective tissue fibers are formed, a watery zone appears about the osteoblasts, and osteoid tissue is defective. Elsewhere in the bones also new bone formation is lacking, whereas bone resorption goes on at a normal rate. The result is rarefaction of bone, similar to that which occurs in senility.

Lesions in the teeth may occur before skeletal lesions are prominent. The gums become swollen and bleed easily. The teeth tend to loosen, and may even fall out, due to rarefaction of alveolar bone. Degenerative and atrophic changes develop also in the substance of the teeth themselves.

Vitamin D

Vitamin D (calciferol, D₂, and 7-dehydro-cholesterol, D₃) is a fat-soluble vitamin which is not only available in food, but may be formed from ergosterol in the skin by ultraviolet irradiation. It is important in calcium and phosphorus metabolism, the part which it plays being to increase calcium absorption from the intestine or to increase phosphorus retention and in turn calcium retention. Thus for action of this vitamin, adequate mineral intake is essential.

Rickets.—Deficiency of vitamin D leads to rickets in growing individuals. In adults the corresponding condition is osteomalacia. Rickets is most common in infancy, but an adolescent form also occurs. Adequate mineral intake and solar radiation, as well as dietary vitamin D, are important in the prevention of rickets.

Rickets is fundamentally a deficient calcification of osteoid tissue and abnormal cartilage involution in growing bones. Enchondral bone growth is disturbed. The excess of uncalcified osteoid tissue results in unusual softness of the bones, which become bent and deformed near the joints. Such deformities are common about the knees (bowlegs), costochondral junctions (rachitic rosary), and thorax (pigeon breast). The most significant gross changes are seen on the cut surface of an epiphyseal region. The tissue is softened, and the normally sharp narrow line of ossification is replaced by a wide irregular zone of soft gray tissue. Histologically, the area shows great disorder of growth with excess osteoid tissue and failure of its calcification. In all parts of the bones there is an excess formation of bone matrix, which remains uncalcified or eventually is poorly calcified. The bone marrow becomes fibrous.

Teeth suffer from the same lack of calcification as in bones, the lesions being in the permanent dentition. There may result dimpling of the enamel, furrows, and other types of defects.

Hypervitaminosis D.—Vitamin D is the only vitamin with which overdosage is known to result in deleterious effects. A very large intake is necessary in man before damage is caused. In experimental animals the main effects are skele-

tal osteoporosis, due to osteoclastic resorption, and calcium deposition in soft tissues, particularly in arteries and in the kidney.⁸

Vitamin E (Alpha-Tocopherol)

Little is known about the pathology of vitamin E deficiency in man. In experimental animals, E deficiency leads to degenerative and atrophic changes in the testes and also severe degenerative changes in skeletal muscles, accompanied by marked cellular infiltrations.

Vitamin K

Vitamin K is necessary for the formation of prothrombin, an essential in the clotting mechanism. Absorption of vitamin K from the intestine is favored by the presence of bile salts. Lack of K causes a hemorrhagic tendency, as noted in obstructive jaundice, and in the hemorrhages of newborn infants:

Biotin

Biotin (vitamin H), a recently isolated member of the vitamin B complex, is a co-enzyme of respiratory metabolism essential to the growth of some bacteria and yeast. Biotin may be synthesized in man by intestinal bacteria. A protein in egg white (avidin) combines with biotin and renders it nonabsorbable. Biotin may have some procarcinogenic action, as it increases the incidence of cancer of the liver in rats due to "butter yellow" (dimethyl-amino-azobenzene). Biotin is not known to have any role in human pathology.

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CHAPTER XI

DISTURBANCES OF GROWTH

The process of growth of cells, tissues, organs, and of the body as a whole presents unsolved problems of great complexity. The disturbances in growth of the body as a whole, i.e., dwarfism, giantism, etc., are hormonal, metabolic, or congenital developmental disturbances and are considered elsewhere (p. 646). Repair of tissue following injury and replacement of tissue lost through normal wear and tear are processes which proceed continuously. The cells and tissues which are least highly organized and differentiated in function and structure (e.g., connective tissues) are most easily replaced. Highly organized structures, such as renal glomeruli or ganglion cells of the central nervous system, are irreplaceable. Between these extremes are all gradations in capacity for regeneration, repair, and response by growth to normal or abnormal stimuli.

Hypertrophy is an increase in size of an organ or a cell. **Hyperplasia** is an increase in number of cells. Enlargement of an organ may be by increase in size or in number of its component cells or structures. Enlargement of the heart is practically always brought about by increase in size of the muscle fibers, which do not become more numerous. Enlargement of a kidney may be accomplished by increase in size of the component nephrons (glomeruli and their tubules), but their number cannot be increased. On the other hand, organs such as the liver, endocrine glands, and lymphoid tissues have little power to increase the size of their cells, but they enlarge by the process of hyperplasia.

Hypertrophy of cells and organs occurs in a variety of physiologic and pathologic conditions. Examples of physiologic hypertrophy are the enlargement of voluntary muscles by exercise, or of the uterus during pregnancy. Compensatory hypertrophy is the enlargement of the residue of an organ or tissue when a portion is removed or destroyed; e.g., if one kidney is removed, the remaining kidney, if normal, enlarges due to increase in size of the individual nephrons (renal counterbalance). The necessity for increased function appears to be the basis of enlargement of an organ, and the term "work hypertrophy" is frequently justifiable. The heart undergoes hypertrophy when greater work is thrown

on it by increased peripheral resistance (hypertension) or by abnormality of valvular function. The final details of the mechanism by which hypertrophy is accomplished are not known, but a sufficient blood supply appears to be a necessity. In the case of the hypertrophy and hyperplasia of the breasts during menstrual cycles and in pregnancy, endocrinal stimulation by hormones from the ovary appears to be the controlling mechanism.

Metaplasia is a change from one type of cell to another. It may be the result of chronic inflammation or irritation, impairment of nutrition and function, or demand for altered function. A common example is a change from columnar or secretory epithelium to a flattened or squamous type. This change may be observed in bronchial mucosa, gall bladder or endocervix as a result of chronic inflammation. Vitamin A deficiency produces a similar metaplasia (see p. 189). Metaplasia also is common in cells of connective tissue type, with the appearance of cartilage or bone in unusual situations such as scars, arteriosclerotic blood vessels, injured and sightless eyes, or in degenerated areas of a goiter.

Anaplasia is a reversion or transformation of cells into a more primitive, embryonic, or undifferentiated type. Such cells have a greater faculty for growth and multiplication but less capacity for specialized function. Anaplasia is an important feature of tumor growth, and in general its degree parallels that of the malignancy of the neoplasm.

TUMORS

A tumor or neoplasm is an overgrowth of cells which are independent of normal growth controls, serve no useful purpose, and are often injurious to normal tissues. It is thus to be distinguished from regenerative, reparative, and inflammatory processes. Tumors are composed of cells and intercellular substances such as may be found in embryonic or mature tissues. Growth activity predominates over function, though the latter is not necessarily lacking. In certain tumors, such as those from endocrine glands, functional activity may be an important feature. Tumors act as parasites, absorbing nourishment from the blood, growing with enhanced vitality at the expense of normal tissues, and yet performing no useful work for the body.

Benign tumors are those which grow slowly and expansively, and unless they are in some vital spot or interfere

with an important organ, they are well tolerated, do not necessarily interfere with the individual's well-being or shorten his life. They are composed of well-differentiated mature types of tissue.

Malignant tumors are more rapidly growing, will infiltrate and extend into normal structures, and unless effectively treated always interfere with health and eventually cause death. They are usually composed of more embryonic or poorly differentiated cells.

Classification of Tumors

Neoplasms are classified according to structure and origin, as etiology is too uncertain to form a satisfactory basis. No grouping seems entirely satisfactory, but the simplest and most common classification divides tumors into the following varieties:

1. Tumors of mesenchymal origin
 - a. Benign
 - b. Malignant—sarcoma
2. Tumors of epithelial origin
 - a. Benign
 - b. Malignant—carcinoma
3. Mixed tumors and teratomas
 - a. Benign
 - b. Malignant

In the first class (tumors of mesenchymal origin) are included not only fibroblastic tumors but also those of cartilage, bone, fat, blood vessels, lymphatic tissue, mesothelium, muscle, and blood forming tissues. The mixed tumors are those arising from multipotential cells and containing more than one type of tissue. Teratomas arise from totipotent cells, contain representatives of all three germ layers, and show attempts at organ formation.

The tumors of particular organs are considered with the other lesions of those organs, where details of classification and structure are presented.

Characteristics of Benign Tumors.—Benign tumors do not endanger life unless they are so situated as to interfere with some vital organ or function. They grow slowly, and after reaching a certain size may remain stationary. Their growth is expansive; they push aside normal tissues but do not invade, and hence they appear as circumscribed, well-demarcated, and even encapsulated growths. They do not metastasize; i.e., secondary tumors are not formed in other organs.

Necrosis and ulceration are less frequent than in malignant tumors. Local removal is usually successful and not followed by recurrence. Histologically, they are composed of a well-differentiated, mature type of tissue, closely imitating the normal tissue of their origin. Rarity of mitoses reflects their slow growth. No sharp line separates benign and malignant tumors, and differences are often a matter of degree. Borderline cases are quite common and often difficult to classify.

Characteristics of Malignant Tumors.—Malignant tumors are those whose unhindered progression invariably leads to death of the individual. They grow rapidly, infiltrating and invading surrounding tissues, so that they are unencapsulated and poorly demarcated. Metastases develop in distant organs. Local removal of a malignant tumor, unless absolutely complete, is followed by recurrence at the same site. They are more prone to degeneration and ulceration than are benign tumors. They may produce cachexia and anemia. Histologically, they are composed of embryonic, primitive, or poorly differentiated cells. There tends to be polymorphism, and unsuccessful imitation of their tissue of origin. Relative frequency of mitosis reflects their rapid growth, and abnormal forms of mitotic nuclei may be present.

The studies of Warburg on the metabolism of tumor cells indicated that they have increased glycolytic powers; i.e., they break down glucose to form lactic acid even in the presence of oxygen, whereas normal cells under similar circumstances form carbon dioxide and water.

It has been noted that malignant cells have nuclei and nucleoli of larger average size than in corresponding non-malignant cells. Cowdry² has listed the characters of malignant cells as follows:

1. A lack of polarity;
2. A wide variation of nuclear and cytoplasmic structure;
3. A decrease in structural differentiation and specific functional activity;
4. A lesser dependence on oxygen supply;
5. A decrease in organismal control over cell division and an increase in autonomy, or self-regulation of cell division;
6. An increase in transplantability within the same species;
7. An increase in invasiveness and ability to outlive cells of invaded tissue.

Estimation of Malignancy and Prognosis.—The factors which must be considered in estimating the result of a malig-

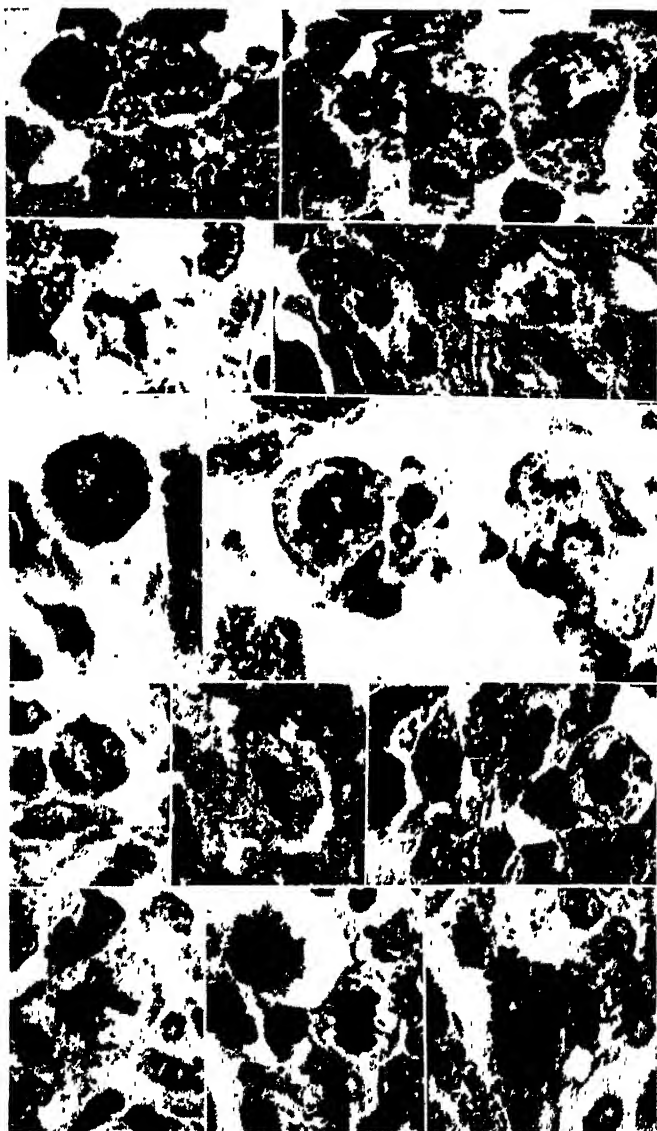


Fig. 71.—Mitotic nuclei. Typical and atypical forms from a rapidly growing carcinoma.

nancy include (1) the type of tumor, (2) its situation, (3) the duration, size, spread, and presence or absence of metastasis, (4) the age and condition of the patient, (5) the rate of clinical growth, (6) the histologic structure, and (7) radiosensitivity of the tumor.

The **type of tumor** is important, since cancers vary in their malignancy and course. Certain tumors, such as the basal-cell carcinoma of the skin, grow slowly and rarely metastasize. At the other extreme are tumors of rapid growth and early extension, such as myeloma of bone and lymphosarcoma.

Situation of a tumor influences the outcome because it may interfere with vital structures, or be such as to make operative removal impossible, e.g., in the case of gliomatous tumors of the brain, or carcinoma of the esophagus.

Duration of the tumor influences prognosis, as it allows time for spread. Thus, a tumor which is easily curable in an early stage, may be hopeless later. **Extensive local spread or metastasis** in other organs suggests an earlier and more inevitable end. On the other hand, long duration of a tumor with but slight increase in size and no metastasis suggests slow growth, low malignancy, and a relatively favorable outcome.

Age is of some importance in that certain tumors seem to progress more rapidly in younger individuals. **Pregnancy and lactation** cause more rapid growth in cancer of the breast.

Radiosensitivity of a tumor is often important in determining how long life may be prolonged, or if cure is possible.

Histologic structure is of importance in indicating the type of tumor, rapidity of growth, and degree of anaplasia or differentiation. Systems of histologic grading have been evolved.

MICROSCOPIC GRADING OF CANCER.—Many factors influence degree of malignancy other than histologic structure. But among tumors of the same type and arising at the same site, there are variations in malignancy which can be correlated roughly with the degree of anaplasia or undifferentiation. Such microscopic grading of the malignancy of a tumor, when put on a numerical and standardized basis, is useful in predicting the course of the disease when used in conjunction with the other factors noted above, such as size, degree of extension, etc. It may also be helpful in determining

the type of treatment likely to give the best results. In general, the greater the anaplasia of a tumor (i.e., the higher the microscopic grade of malignancy), the greater is the radiosensitivity.

Broders³ originated and popularized a method of grading according to which tumors are divided into four grades of malignancy, as follows:

Grade I—tumors showing a marked tendency to differentiation, with three-fourths or more of their cells differentiated:

Grade II—three-fourths to one-half of the cells differentiated;

Grade III—one-half to one-fourth of the cells differentiated; and

Grade IV—one-fourth to none of the cells differentiated.

While this system of grading is generally useful, it is often extended and modified in the case of tumors of certain organs, e.g., cervix uteri or rectum. The various modifications are noted later as these tumors are considered.

The Effects of Irradiation on Tumors.—The effects of x-rays and radium on tissues are similar. Only the gamma rays are used in therapeutic work. The alpha and beta rays, which are more destructive but less penetrating, are excluded by screening. All tissues, normal and neoplastic, are affected by irradiation, so that radiosensitivity is a relative term. Cells which are actively proliferating or which are of primitive type are more sensitive than normal tissues, so that there is usually a considerable margin between doses which are damaging to neoplastic and to normal tissue.

The effects of gamma rays on growing cells vary with the intensity and duration of exposure, and consist of (a) destruction of some cells, (b) inhibition of imminent mitosis, followed by abnormal mitosis and disruption of the cells, and (c) damage to resting cells so that continued proliferation fails. Cells in a premitotic phase are believed to be particularly susceptible, though this has been questioned.

Irradiation also may have effects which are not directly on the cells. Action on blood vessels supplying tumor tissue may be of importance. An early effect of irradiation is extreme hyperemia due to distention of capillaries, and this may be followed by thrombosis or rupture. Larger blood vessels may be completely obliterated. The effect on the tumor bed has been stressed by Cramer⁴ as contributing to the effects of irradiation on tumor tissue.

RADIOSENSITIVITY OF TUMORS.—Since all tumors can be affected by irradiation, the terms radiosensitivity and radioresistance are but relative. Radiosensitivity does not necessarily imply curability by irradiation. Some highly radiosensitive tumors, such as lymphosarcoma, are rarely curable by irradiation. Other tumors which are radioresistant may be curable. Easy accessibility and tolerance of surrounding structures are important factors in curability. Irradiation may be valuable in relief of pain, e.g., in skeletal metastasis from carcinoma of the breast, even though not curative.⁵

Radiosensitivity varies with the reproductive activity of the tissue (Law of Bergonié and Tribondeau) and increases with increasing anaplasia and embryonal quality of tumor cells. The tumor bed is also important; a bed of slight vascularity or of fat, bone, or cartilage is unfavorable. Tumor recurrences tend to be more resistant than was the original tumor. The presence of infection in the tissue appears to decrease sensitivity.

Warren⁶ has divided tumors into three groups according to their radiosensitivity:

- I. Radiosensitive tumors—those which regress or clinically disappear with a dose of 2,500 r. (roentgen units) or less, usually without appreciable damage to adjacent normal tissue. In this group are lympho-epithelioma, lymphomatous tumors, Ewing's tumor of bone, and chronic leucemia.
- II. Radioresponsive tumors—those which require 2,500 to 5,000 r. for similar regression. Adjacent normal tissue shows definite reaction to this dosage, but without permanent injury. Examples of this group are basal-cell carcinoma of the skin, carcinoma of the cervix, and adenocarcinoma of the thyroid.
- III. Radioresistant tumors—those which require over 5,000 r. for response. Damage to normal tissue may equal or exceed that done to the tumor. Malignant melanoma, neurogenic sarcoma, and osteogenic sarcoma are radioresistant.

Spread and Metastasis of Tumors.—Malignant tumors spread by direct invasive growth into surrounding tissues, and by the formation of secondary tumors not connected with the original neoplasm. This latter process, which is called metastasis, is due to extension by lymphatics, by the blood stream, and by implantation.

Lymphatic metastasis is the common method of spread of carcinoma. Tumor cells grow into lymphatic channels, are broken off and carried as emboli to a lymph node. Here the tumor cells lodge and can often be seen in the subcapsular space or peripheral sinus. Thus a secondary tumor is started, which may eventually overwhelm the node, break through the capsule, and spread locally as well as onward in the lymphatic system.

Sampson Handley pointed out that there also may be lymphatic spread by permeation, i.e., by direct and continuous growth along a lymphatic channel. This was emphasized particularly in the spread of cancer of the breast. While lymphatic permeation probably occurs, lymphatic embolism appears to be more common.

Metastasis by the blood stream is the common method of spread of sarcoma, but many carcinomas spread in this fashion as well. Tumor cells penetrate the thin wall of a vein, are broken off and carried away as emboli. Tumor emboli that enter branches of the portal vein lodge in the liver, and that organ is the common site for metastasis from tumors of the intestinal tract. Tumor emboli from systemic veins tend to lodge in the lung. Undoubtedly some tumor cells reach the arterial circulation directly or by passage through pulmonary capillaries.

Metastasis by implantation occurs when tumor cells involving a serous or mucous membrane become detached and later implanted on other areas. Carcinoma of the ovary commonly spreads throughout the peritoneal cavity in this fashion. When cancer involves a serosal surface, considerable fluid is usually present in the cavity and often is of a hemorrhagic character. Tumor cells may be demonstrable in such fluids by centrifuging and making paraffin sections of the cellular material thus thrown down.

Metastatic tumors are uncommon in certain tissues, such as voluntary muscle, heart, and spleen. Blood-borne metastasis involves mainly liver, lung, and bone. Metastatic tumors of brain are most commonly from the lung, breast, stomach, prostate, and adrenal. Those tumors which metastasize to bone with particular frequency are hypernephroma of the kidney and carcinomas of the prostate, lung, ovary, breast, testis, and thyroid.

Cachexia.—Wasting of marked degree and severe anemia are common in late stages of malignant disease, but are far

from an invariable occurrence. Cachexia is often influenced by starvation in the case of tumor in the alimentary tract, and by infection. There is no evidence of a specific toxin or poison from cancer tissue.

Causes of Death in Malignant Diseases.—The immediate cause of death in cancer is most commonly a pulmonary disorder, such as pneumonia, embolism, abscess, atelectasis, etc. Cachexia appears to be the most frequent single cause and is particularly common with cancer of the breast, stomach, and colon. Renal failure is common with carcinoma of the cervix, bladder, and prostate.⁸ Tumors of the alimentary tract may cause death by obstruction. Intracranial tumors cause death by pressure effects within the rigid casing of the nervous system.

The Experimental Study of Tumors

The chief advances of experimental cancer research hinge on three discoveries; (1) that certain tumors are transplantable from animal to animal within a given species, (2) that malignant tumors can be initiated by the use of chemical

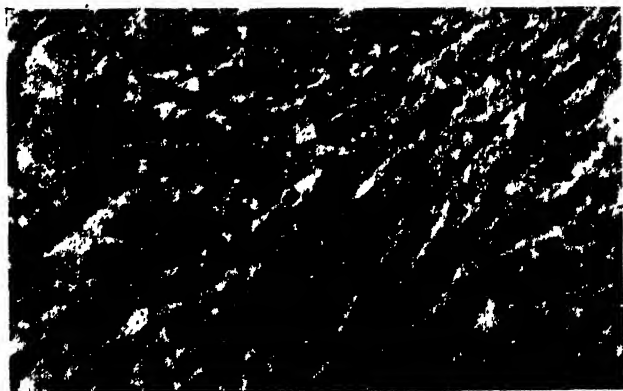


Fig. 72.—Sarcomatous tumor induced by methyl cholanthrene.

“carcinogenic” agents, and (3) that certain tumors, e.g., the chicken sarcoma of Rous, can be transferred by means of a cell-free filtrate or extract and are apparently of viral etiology. Further facts have been gleaned by observation of tumors grown in tissue culture, and breeding experiments with animals have thrown light upon hereditary and other factors in tumor incidence.

The transplantability of tumors in mice and rats was discovered early in this century by Loeb and Jensen. Transplantability varies greatly in different tumors and is usually successful only with animals of the same species. Only the intact tumor cells grow, and in the new host the tumor cells are direct descendents of the original malignant cells; i.e., no new tumor is formed and the process is comparable to metastasis.

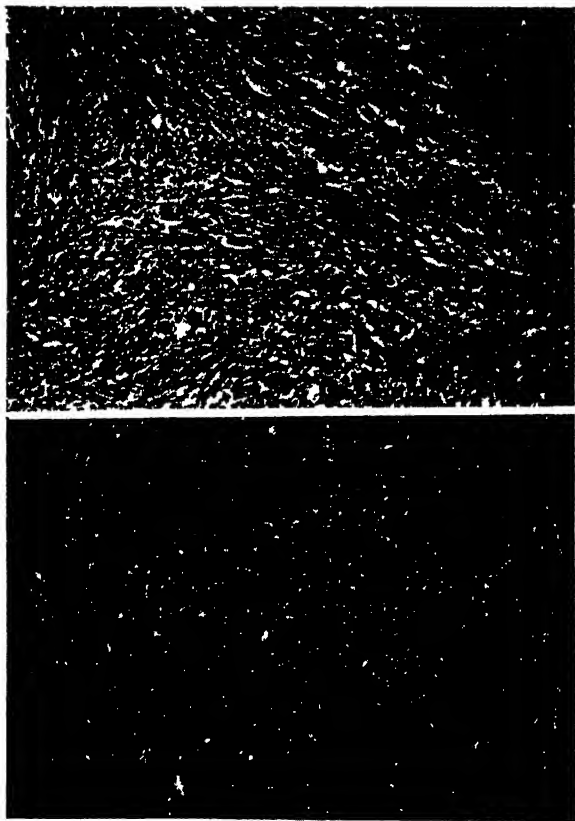


Fig. 73.—Rous sarcoma.

The production of cancer by chemical irritation or stimulation was achieved by Yamagiwa and Itchikawa, who found that repeated painting of the skin of rabbits with tar

resulted in carcinoma. Previous knowledge of occupational cancers suggested that such a result might be expected. Paraffin or tarworkers and chimney sweeps were known to be peculiarly subject to the development of squamous-cell carcinoma of the skin. Isolation of the chemicals in tar responsible for the carcinogenic action was the work of Kennaway and his associates.¹⁰ The potent carcinogens were found to be polycyclic hydrocarbons, among the most powerful of which are 1:2:5:6 dibenzanthracene, methyl cholanthrene, and 3:4 benzpyrene. These compounds have a chemical relationship to certain naturally occurring substances, such as deoxycholic acid, estrogen, and sterols. There is some evidence that endogenous cancer-producing agents may exist. Carcinogenic extracts have been obtained from human tumors, but the nature of the agents is as yet unknown.¹¹

Rous discovered a sarcoma, the causative agent of which could be transmitted to chickens by means of a cell-free and bacteria-free filtrate. It is well established that the Rous sarcoma and other similarly transmissible tumors of fowl are of viral origin. Other tumors of fowl, and a mammalian tumor, a papilloma of the skin of rabbits discovered by Shope, are of viral origin, but there appears to be no direct evidence that viruses are etiologic agents in human tumors.

Heredity as a factor in cancer has been suspected from the high incidence in certain families. In certain types of tumors, such as neuroblastoma of the retina and multiple polyposis of the colon, inheritance appears to be of importance. Breeding experiments with mice, in which strains were produced having a very high incidence of cancer of the breast, pointed in the same direction. However, extra-chromosomal factor also are at work here, for the incidence is influenced by estrogenic hormones and by a "milk factor," i.e., a substance in the mother's milk which has many properties of a virus and influences the development of breast cancer.

The Causation of Cancer

Ewing has stated that cancer should be regarded, not as a single disease, but as a group of diseases in which there may be etiologic multiplicity. Cramer¹² has emphasized that the etiology of cancer has to be considered as a separate problem for each organ. Many causative factors are known, but a single ultimate cause of all forms of cancer has so far

eluded discovery. Probably cancer should be regarded as a form of tissue reaction to a variety of stimulating injuries.

Cohnheim developed a classical theory of etiology of tumors based upon "rests" of fetal cells. According to this theory, misplaced or superfluous embryonic cells failed to proceed to full development, remained dormant for a period, and then with recommencement of growth resulted in a tumor. The theory was extended by Ribbert who suggested that the misplacement of the cells put them beyond the normal controls of growth, thus allowing their lawless proliferation. These theories seem applicable to certain tumors, such as the embryoma or mixed tumors of the kidney (Wilms'), but their general applicability is doubtful. Displacement of tissue will not in itself result in a tumor.

Parasites as a cause of certain tumors in animals appear to act by causing chronic irritation. There is little evidence that parasites or bacteria are important in human cancer. An exception to this is that *Schistosoma haematobium*, a parasite common in Egypt, produces chronic irritation in the urinary tract and a high incidence of cancer of the bladder.

Viruses are established as a cause of some neoplasms in animals, but evidence that they are a factor in human cancer is incomplete.

Trauma or mechanical injury often seems to have some relationship to development of tumors, especially in testis, bone, or in breast. However, it has not been unquestionably established that it is a factor of frequent or direct importance.

Heredity has been mentioned as a noteworthy influence in certain types of cancer. In most cases it is probably only a predisposition, or background of susceptibility, on which other causes must be superimposed. Experimentally, heredity has been shown to be important in influencing the type and site of malignancy, and the age at which it occurs.¹⁵

Mesenchymal Tumors

The benign mesenchymal tumors are named according to the type of tissue from which they arise, e.g., fibroma, from fibrous connective tissue, lipoma from fat, myoma from muscle, etc. The malignant connective tissue tumors, or sarcomas, may be undifferentiated, or may be so well differentiated that their tissue of origin is recognizable, e.g., fibro-

sarcoma, liposarcoma, etc. The following forms of connective tissue tumors are listed for purposes of description:

ORIGIN OR TYPE OF CELL	BENIGN FORM	MALIGNANT FORM
fibrous connective tissue	fibroma	fibrosarcoma
peripheral nerve sheaths	neurofibroma	neurogenic sarcoma
fatty tissue	lipoma	liposarcoma
myxomatous tissue (as in umbilical cord)	myxoma	myxosarcoma
cartilage	chondroma	chondrosarcoma
bone	osteoma	osteogenic sarcoma
muscle	myoma	myosarcoma
smooth	leiomyoma	leiomyosarcoma
striated	rhabdomyoma	rhabdomyosarcoma
notochord	chordoma	
lymphocytic tissue	lymphoma	lymphosarcoma
serous linings		mesothelial sarcoma
blood or lymph vessels	angioma	angiosarcoma
neuroglia	glioma	gliosarcoma
		Undifferentiated sarcoma
		—small round-cell sarcoma
		—large round-cell sarcoma
		—mixed-cell sarcoma

Fibroma.—Fibromas are derived from and composed of fibrous connective tissue and are of wide distribution. Most commonly they are found in connection with skin, subcutaneous tissue, fascia, or tendons, but also in certain organs, such as the ovary, kidney, breast, and intestine. With slow and expansive growth, they tend to encapsulation. Microscopically, they are composed of interlacing bundles and fibers of collagenous connective tissue.

Desmoid is a fibroma arising in musculo-aponeurotic structures, particularly frequent in the lower anterior abdominal wall. Trauma seems to be a predisposing factor, and most cases have occurred in women who have borne children. There may be local infiltration of muscle, but sarcomatous transformation and metastases do not develop.¹⁴

Keloid is an excessive formation of a fibrous scar resulting in a tumor-like mass resembling a fibroma. Certain individuals, particularly among the Negro race, are prone to this excessive fibrosis following injuries of the skin. Microscopically, the keloid consists of dense bundles of collagenous and hyalinized connective tissue (see Fig. 298, p. 637).

Fibrosarcoma.—Fibrosarcoma is a malignant tumor tending to differentiate in the direction of fibrous connective tissue. It occurs at any age, but the highest incidence is in the fifth and sixth decades. The most common site of origin

is in the extremities, particularly the lower, but the origin may be from connective tissue in any region. Fibrosarcoma appears as a rounded, lobulated tumor, often appearing circumscribed or encapsulated, and hard and fibrous, or soft and friable, depending on the amount of fibrous tissue which has been formed. Areas of degeneration, necrosis, myxomatous change or cyst formation may be present. Simple



Fig. 74.—Multiple neurofibromatosis (molluscum fibrosum). (From Sutton and Sutton: Diseases of the Skin, courtesy Dr. Emil Theilman.)

excision is often followed by recurrence. Following repeated recurrences, death may result from visceral metastasis, or from infection and hemorrhage of the ulcerating tumor. The malignancy tends to be proportional to the number of mitotic nuclei and tumor giant cells, and to the scarcity of collagen fibers.^{16, 17}

Neurofibroma.—Neurofibromas (neurinoma, neurilemma) are connective tissue tumors arising from the sheaths

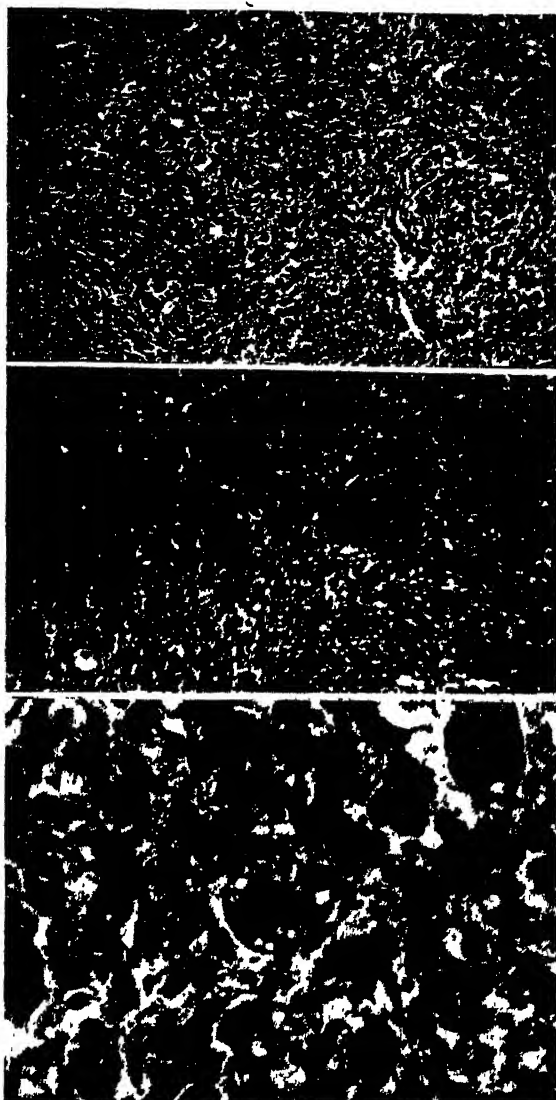


Fig. 75.—Polymorphic fibrosarcoma. Note the tumor giant cells, and the hyperchromatism. Low, medium, and high magnification.

of cranial or peripheral nerves. Of the cranial nerves, the eighth is most commonly involved, the tumor being found in the cerebellopontine angle (acoustic neurinoma). The exact origin of the peripheral nerve sheath tumors, e.g., from the sheath of Schwann, endoneurium, neurilemma, etc., has been a subject of discussion in recent years, and the terminology used has varied depending on the favored theory. Discussions of these problems are found in the papers of Foot,¹⁸ and Bailey and Hermann.¹⁹

Von Recklinghausen's disease is a familial form of multiple neurofibromatosis. Neurofibromas are found on branches of the cutaneous nerves, and along nerve trunks of the thorax, brachial and lumbar plexus, and extremities. Cranial nerves and spinal nerves within the spinal canal are sometimes involved as well. Coffee-colored areas of skin pigmentation are common stigmas of this disease. The tumors are benign encapsulated neurofibromas and usually do not destroy the nerves from which they grow. In a small proportion of cases, one or more of the tumors may become malignant.²⁰

Neurogenic Sarcoma (Neurogenous Sarcoma).—Sarcomatous tumors of soft tissue may be found in distinct relation to nerves. More often such relationship is not demonstrable, and in such cases the features suggesting a neurogenous origin are (1) arrangement of the cells in definite bundles with an interlacing pattern of the herring-bone type, (2) wavy, fine, elongated nuclei which tend to line up in parallel fashion to form rows (palisading), and (3) fibrils, demonstrable by silver stains, distributed in pericellular fashion.

The proportion of sarcomas of skin and subcutaneous tissues which are of neurogenous origin is a matter of debate. Ewing and others have held that the majority of such spindle-cell sarcomas arise from peripheral nerves. From a practical standpoint, the criteria of degree of malignancy and the prognosis are the same for neurogenic sarcoma and fibrosarcoma, varying with the number of mitoses and tumor giant cells, and the scarcity of fibers.

Lipoma.—Lipomas are benign, circumscribed masses of an adult type of fat tissue. They occur in many situations, but especially in the subcutaneous tissues of the back or shoulder region. In some cases they are multiple, grow to large size, and appear to have a familial factor in their causation. In certain rare instances they show a connection with nerves and are painful.²¹ Microscopically, they are composed of fat cells of the usual type found in adipose tissue, though of a larger average size.

Liposarcoma.—Liposarcoma is a rare type of tumor composed of embryonic fat cells containing small fat globules in their granular cytoplasm. Much of the tumor may be undifferentiated and highly cellular. In some areas mature types of fat cells may be found.

There are two types of liposarcoma. One variety, the adult form of liposarcoma, is composed of granular cells resembling those found in chronic inflammation of fat tissue. Trauma to fatty tissue often seems to precede this type of tumor. The second type is an embryonal liposarcoma (myxoliposarcoma). This tumor contains many tiny proliferating blood vessels, mucus-producing cells, and some embryonal fat tissue.



Fig. 76.—Lipoma of axilla. (Courtesy Dr. H. C. Schmeisser.)

Liposarcomas occur most often around the buttocks, lower limbs, and in the retroperitoneal spaces.²² They occur as a relatively common type of soft tissue tumor in infancy and childhood and are quite radiosensitive.²³

Myxoma.—This tumor is a modified form of fibroma, in which a mucoid intercellular substance separates embryonic connective tissue cells, so as to resemble in appearance the tissue of the umbilical cord. A pure myxoma is rare, but a

myxomatous change or degeneration in a portion of some other type of connective tissue tumor is not uncommon.

Myxosarcoma is likewise rare as a pure tumor.

Tumors of Bone.—**Chondroma**, **chondrosarcoma**, **osteoma**, and **osteogenic sarcoma** are tumors which usually arise in connection with skeletal structures and are considered in Chapter XXIV.

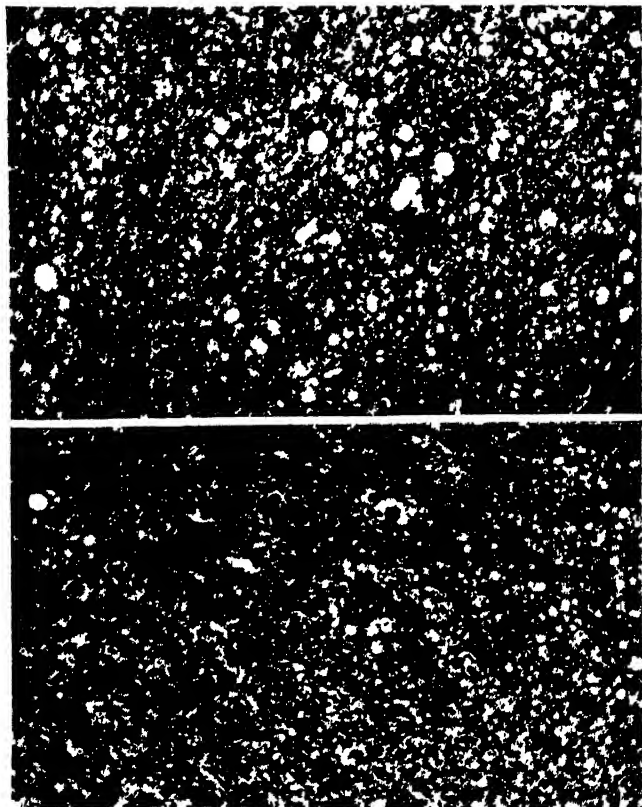


Fig. 77.—Liposarcoma. Note that some of the tumor cells have differentiated into mature or adult types of fat-holding cells.

Myoma.—Benign tumors of muscle are of two types: **rhabdomyoma**, an extremely rare tumor of striated muscle, and **leiomyoma**, a very common tumor composed of smooth muscle. Leiomyomas are most frequent in the uterus, where

they have an abundant fibrous stroma, and are commonly called "fibroids" (see p. 591). They also occur in many other situations where smooth muscle is normally found, as in the intestinal tract. Malignant transformation of a uterine myoma to a leiomyosarcoma may occur. A pure rhabdomyosarcoma is very rare, but striped muscle fibers are some-

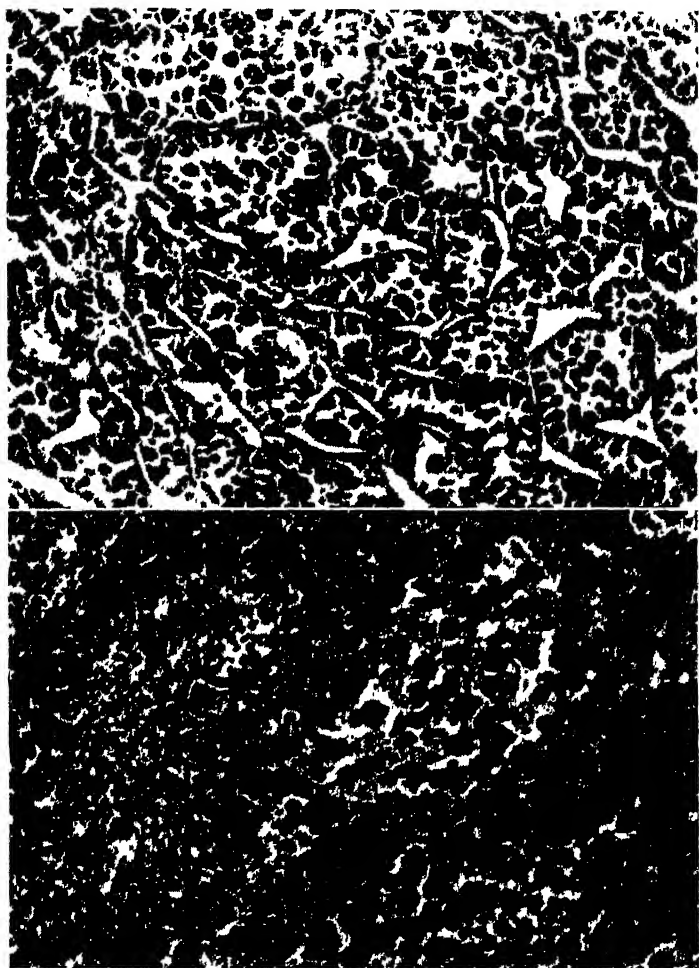


Fig. 78.—Granular cell myoblastoma of thigh. (From a section of Dr. H. N. Allen.)

times found in malignant mixed tumors such as those of the kidney (p. 326) and uterus (p. 594).

The so-called *granular cell myoblastoma* is an uncommon tumor which has been interpreted as derived from primitive myoblasts. Most examples have been found in the tongue, but some have appeared in skin, skeletal muscle, and other

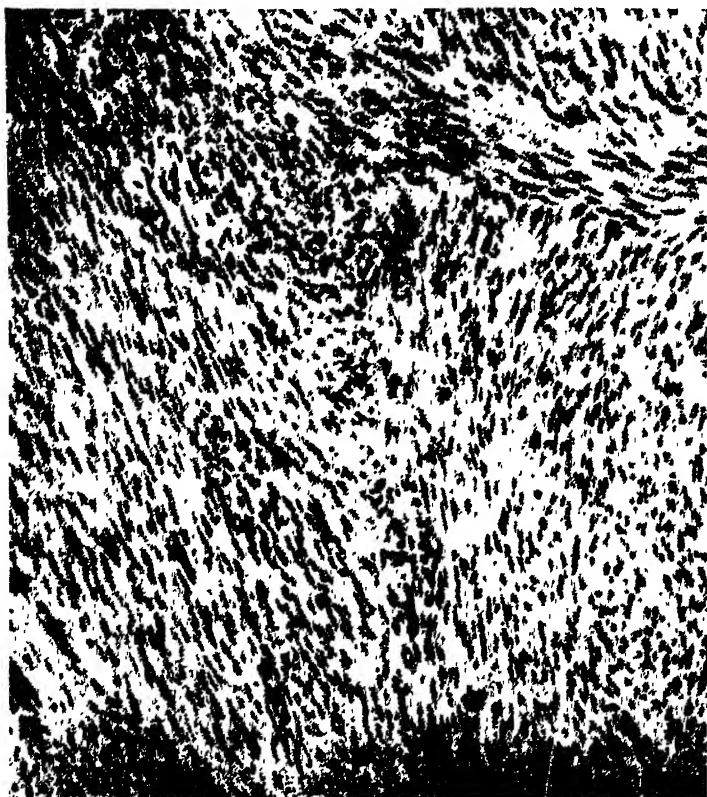


Fig. 79.—Leiomyoma of small intestine.

sites. They are composed of large polyhedral cells with small nuclei and an abundant, pale, granular cytoplasm. Cross striations and structures resembling myofibrils have been observed in some cases. The tumor may be encapsulated, but in most instances is locally infiltrative.^{24, 25}

Chordoma.—Chordoma is a rare tumor which arises from notochordal remnants at the upper or lower ends of the vertebral column. It is composed of large, clear, closely packed cells having a vacuolated cytoplasm (see p. 688).

Lymphomatous Tumors.—Lymphoma, lymphosarcoma, reticulum-cell sarcoma, and other tumors of lymphoid, reticulo-endothelial, and blood forming tissues are considered in Chapter XVI.

Mesothelioma.—Mesothelioma is a malignant tumor arising from serous surfaces such as the pleura, pericardium, and peritoneum (see p. 372).

Angioma.—Tumors composed of endothelial cells tending to form blood or lymphatic channels consist of both benign and malignant forms. They are considered on p. 242.

Glioma.—The gliomas are tumors arising from the neuroglial or supporting cells of the central nervous system (see p. 688).

Undifferentiated Sarcoma.—Many of the malignant mesenchymal tumors fail to differentiate into recognizable types of cells and are given descriptive designations such as small round-cell sarcoma, large round-cell sarcoma, mixed-cell sarcoma, and spindle-cell sarcoma. Mitoses are numerous in these highly malignant growths.

Small round-cell sarcoma arises in a variety of sites and tends to be rapid in growth and metastasis. It forms a fairly well-demarcated pinkish-white fleshy mass, in which areas of degeneration and hemorrhage are common. Microscopically, it is composed of small, round, uniform cells among which are abundant thin-walled blood vessels. The **large round-cell sarcomas** are similar grossly but are composed of cells that are larger, less uniformly round, and with more abundant cytoplasm. Many of the tumors designated as small and large round-cell sarcomas are in reality lymphosarcomas and reticulum-cell sarcomas. The **mixed-(polymorphic) cell sarcomas** are made up of cells having variable size and shape, often with bizarre tumor giant cells.

Spindle-cell sarcoma shows some differentiation toward recognizable fibroblastic cells. The tumor is somewhat harder in the gross, less prone to degenerative changes, and less malignant than the round cell forms. It is composed of bundles of elongated spindle-shaped cells with oval nuclei. When the elongated cells are cut transversely, they appear rounded and with but scanty cytoplasm.

General Characteristics of Sarcoma.—Malignant mesenchymal tumors are more prone to occur at any age through-

out life than are carcinomas. During the first few decades of life they have a much higher relative frequency than malignant epithelial tumors. They tend to be soft, and of fleshy appearance and consistency, except in the highly differentiated types. Hemorrhages and degenerative changes are common in the tumor tissue. They usually have abundant, thin-walled blood vessels, which are intimately associated with the tumor cells, whereas in epithelial tumors the blood vessels are contained in the stroma which separates groups of tumor cells. The thinness and intimacy of vessels in sarcomas readily enable the tumor cells to grow through their walls. Hence they commonly metastasize by way of the blood stream, the lung being the most frequent site for secondary tumors. Lymph node metastasis also occurs in 5 to 10 per cent of sarcomas.²⁸

Epithelial Tumors

Tumors derived from and made up of epithelial tissues may be classified into two groups, the benign and the malignant (carcinoma). An epithelial tumor, like normal epithelial tissue, has a connective tissue stroma which supports the epithelium and in which are contained blood and lymphatic vessels. Insufficiency of this stroma on which nutrition depends results in degenerative changes and necrosis in the tumor. On the other hand the stroma may progress equally with the growth of the epithelial elements, or even exceed it, producing fibro-epithelial tumors (e.g., fibroadenoma of the breast), or in the case of carcinoma, scirrhous tumors.

BENIGN EPITHELIAL TUMORS

Benign epithelial tumors are of two main types: papilloma, which grows outward from an epithelial surface, either cutaneous or mucous, and adenoma, which is derived from and imitates glandular epithelium. The benign tumors progress slowly. By their expansile growth they compress surrounding tissue but do not infiltrate and never form metastases. The cells tend to conform closely to a normal appearance.

Papilloma.—In a papilloma, the tumor cells are situated externally, elevated from the surface, and arranged around a central core of connective tissue containing blood vessels. The surface of a papilloma is exposed to injury by pressure or friction, so that ulceration, infection, and inflammatory

changes are common. The main feature distinguishing them from carcinoma is that the tumor cells do not penetrate the tissues.

Papillomas may originate from skin, mucous surfaces, or the lining of cysts. Cutaneous papillomas may be true tumors, but a group of inflammatory growths of the skin are also loosely called papillomas. The latter include venereal warts (condylomas), the common warts of children (verruca vulgaris) which are of infectious origin, and pyogenic granulo-ma, an excessive growth of granulation tissue.

The true papilloma of the skin is a hard rough tumor with a broad base which may be several centimeters in diameter. The surface is rough and fissured, often with marked keratinization of the superficial cells. When keratinization is excessive, they may be called cutaneous horns.

Some papillomatous tumors of the skin are pigmented and may be confused with true melanomas. They have the structure of an ordinary cutaneous papilloma, but with abundant melanin in the epidermal cells.

Papillomas from mucous surfaces often have long delicate processes attached around a thin central stalk. This type is seen in its typical form in the bladder. Another variety consists of a single thick finger-like process. This type characteristically occurs in the intestine, sometimes in large numbers. Papillomas of mucous surfaces are often called polyps. Multiple polyposis of the large intestine is a familial or hereditary condition in which a malignant change in one or more of the tumors eventually occurs.

Intracystic papilloma, in which the projection of the tumor is into the cavity of a cyst, is seen particularly in cystic tumors of the ovary and of the breast.

Adenoma.—An adenoma is a benign tumor derived from glandular or secretory cells. It has usually a slow rate of growth, a well-defined margin, and quite accurately reproduces the tissue from which it is derived. The tumor cells may function and produce a secretion similar to, or the same as produced by, the normal glandular tissue. Thus mucin tends to be produced in intestinal growths, colloid in thyroid adenomas, and bile in liver adenomas. In the case of adenomas made up of endocrine tissue, excessive secretory activity may result in clinical evidence of hyperactivity of the particular endocrine gland. Distention with secretory material and cyst formation is also a common result of functional activity (cystadenoma).

Since any glandular tissue may give rise to tumor, adenomas are of extremely varied structure. Those which grow within the substance of a gland tend to be rounded and encapsulated. Those which grow from the secretory cells of a mucous membrane, such as endometrium, tend to be polypoid and pedunculated.

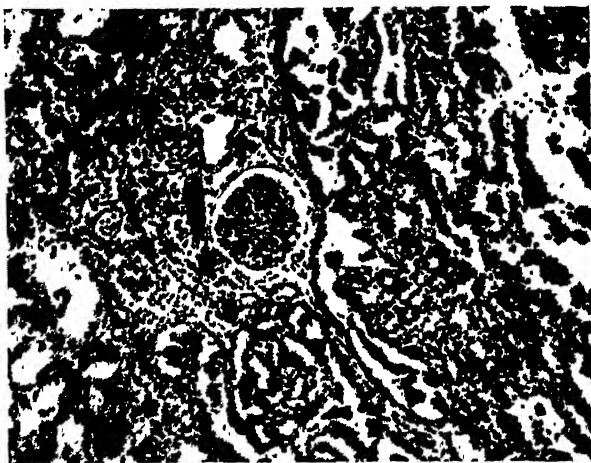


Fig. 80.—Adenoma of kidney. The edge of the tumor is shown, so that a glomerulus and tubules are evident in the left half of the figure.

MALIGNANT EPITHELIAL TUMORS

Carcinoma.—Malignant epithelial tumors form a most important group because of their numerical frequency and serious effects. They vary widely in rate of growth, degree of anaplasia or differentiation, and in gross and microscopic appearance. They are distinguished from benign epithelial tumors in that they invade and destroy normal tissue, and usually will spread by metastasis.

Carcinomas differ in the degree to which they imitate their tissue of origin. In some cases the resemblance to normal tissue is very close, with well-formed glands, tubules, or lining epithelium. At the other extreme, there may be so much anaplasia or reversion to an embryonic type of tissue that the origin of the tumor or even its epithelial nature is difficult to determine.

The stroma likewise is variable. Invading carcinoma cells utilize the existing stroma of the destroyed tissue. When the tumor growth is rapid, the connective tissue and blood vessels are often inadequate to support and nourish the tumor, so that degeneration and death of tumor cells result.

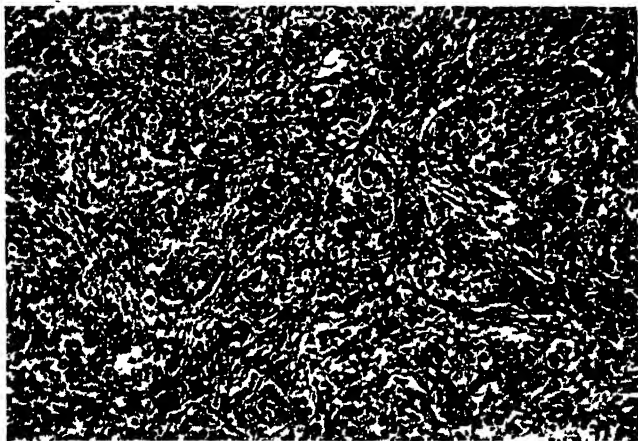


Fig. 81.—Carcinoma. Note the variations in the size, shape, and intensity of staining of the tumor cells. Normal architecture is completely lost.

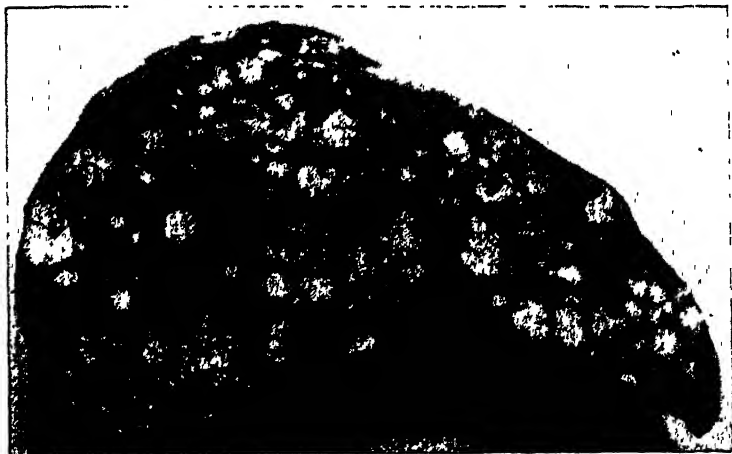


Fig. 82.—Metastatic carcinoma in the liver. (Primary in stomach.)
(Courtesy Dr. H. C. Schmeisser.)

Other tumors (scirrhous) tend to stimulate the growth of the connective tissue stroma, sometimes to exceed the development of the epithelial elements, many of which may be choked off and killed.

A number of terms are used in the classification and description of carcinomas. **Squamous-cell carcinoma** (epithelioma) arises from surface epithelium such as skin, mouth, lip, or cervix, and is made up of squamous epithelial cells. It may also arise from the esophagus, anus, larynx, nose, sinuses, renal pelvis, ureters, bladder, and bronchi. It is most easily identified by the presence of prickly cells or keratinization. **Adenocarcinoma** is a tumor with cells having a glandular or adenomatous arrangement. The terms scirrhous, medullary, and mucoid or gelatinous refer to their gross and microscopic appearance. A **scirrhous carcinoma** is hard and fibrous because of abundant stroma. A **medullary carcinoma** is soft, and brain-like in consistency, because of little connective tissue stroma. **Mucoid or gelatinous carcinomas** are soft and translucent, due to accumulation of a mucoid or colloid material. Carcinomas are frequently not uniformly scirrhous, medullary, or mucoid throughout their whole substance. **Carcinoma simplex** is a carcinoma of glandular tissue in which the cells are arranged in solid cords and masses.

Mixed Tumors and Teratomas

Most tumors are composed of cells of one type, e.g., glandular epithelium as in simple adenoma. However, there are tumors in which tissues of different character occur together in the same growth, and these are classified as mixed tumors or teratomas.

Mixed tumors are derived from pluripotential cells, i.e., cells capable of differentiation into more than one type of tissue. Such tumors are most common in the salivary glands (mixed tumor of parotid, p. 460), and kidney (Wilms' tumor or embryoma, p. 326). In these tumors both epithelial and connective tissue elements are commonly present, but recognizable organs are not found.

A **teratoma** is a tumor containing organs or distinct fetal structures representing all three primitive layers of blastoderm. It is really an attempt at development within one individual of another individual of the same species. They are derived from totipotential cells, i.e., cells capable of differentiation into any organ or tissue, and which in the right



PLATE VII.—Squamous-cell carcinoma of skin. Enlarged 35 times. Note the irregular downward invasion of the squamous epithelial cells, which are fairly well differentiated and are forming numerous keratin "pearls." (From McCarthy, Lee: *Histopathology of Skin Diseases*, St. Louis, The C. V. Mosby Company, 1931.)

circumstances and environment would develop into a complete individual.

Teratomas may arise from either (1) the totipotential cells of the ovary or testicle, or (2) from an undeveloped "rest" of cells of the morula prior to the differentiation of the primitive layers. They most commonly arise in the ovary or testicle, where from some unknown stimulus one of the unfertilized cells begins to grow and attempts to form a new individual. In the ovary these tumors are common and are usually cystic (dermoid cyst), but may be solid.

Those teratomas which arise from "rests" of undifferentiated tissue are most common near the growing ends of the body, in the sacrococcygeal region or at the base of the skull. They may, however, arise in almost any situation. This type of teratoma is closely related to the various types of joined twins and parasitic fetuses.³⁰

Teratomas are relatively benign tumors, causing trouble mainly by their local expansion. Occasionally one type of cell in a teratoma becomes malignant, and metastases are made up of this type of cell alone.

CYSTS

A cyst is a cavity containing fluid and surrounded by a definite wall. There is usually an epithelial lining. The many varieties of cysts can be fitted into the following classification:

1. **Retention cysts** are due to blockage of ducts or tubules, with cystic distention of the proximal portion. Cysts of the kidney and pancreas are usually of this type.
2. **Cysts due to developmental errors** include those arising from the branchial clefts, thyroglossal duct, and from remains of the Wolffian duct (hydatids of Morgagni). Also of developmental origin are the sebaceous cysts of the skin, cystic hygromas (see p. 243), and the cysts associated with spina bifida (see p. 697).
3. **Cystic tumors or cystomas** (cystadenomas) arise very commonly from the ovary, thyroid, and other organs.
4. **Cysts from serous cavities** arise by outpouchings from bursae and tendon sheaths (e.g., ganglion—see p. 673).
5. **Parasitic cysts** include those due to the *Taenia echinococcus* (hydatid cysts), amebiasis, and torula.
6. **Pseudocysts** are those formed as a result of hemorrhagic material (hematoma) which has become encapsulated. Also to be included here are the cyst-like spaces formed as a result of mucinous degeneration.

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CHAPTER XII

THE CARDIOVASCULAR SYSTEM

The circulatory system, which includes the heart, blood vessels, and lymphatics, is concerned with the essential nutrition of tissues. Disease of this system probably outranks in frequency and importance the infectious diseases and cancer.

DISEASES OF BLOOD VESSELS AND LYMPHATICS

Generally speaking, lesions of blood vessels are important in proportion to the degree to which they reduce circulation to vital tissues. Such an effect is most commonly produced by a hardening and thickening of arterial walls referred to as arteriosclerosis. Arteries and veins are also subject to inflammations (arteritis and phlebitis), dilatation (aneurysm and varicosity), and neoplasm (angioma). Thrombosis, embolism, and hemorrhage are important accompaniments of vascular diseases.

Structure of Arteries

Arterial vessels are composed of three coats: intima, media and adventitia. The *intima*, or inner layer, consists of a lining layer of endothelial cells, beneath which are a few muscle and connective tissue fibers. The *media* is formed by muscular and elastic tissue. A condensation of the elastic tissue at the inner margin of the media forms the internal elastic lamella. This inner elastic band frequently appears wavy, due to post-mortem contraction of the vessel. A less definite outer condensation of elastic tissue sometimes forms an external elastic lamella. The *adventitia*, or outer wall, contains a loose network of connective tissue and elastic fibrils, carrying blood vessels (*vasa vasorum*) and nerves to supply the vessel wall.

Winternitz¹ has recently demonstrated that the vascular supply to the wall of blood vessels is richer and more extensive than previously suspected. Small vessels supplying arterial walls are much more numerous in older individuals, and in the presence of arteriosclerosis. They cannot be seen in ordinary sections for reasons discussed by Stern.² Intimal

vasa vasorum are common in arteriosclerotic vessels, but their presence in a normal intima is disputed.

Arteries may be divided into three main classes, according to size and structural variations: elastic arteries, muscular arteries, and arterioles. The group of elastic arteries includes the largest vessels, the aorta and its immediate branches. In this group the vessel wall contains elastic tissue in greatest proportion. Elastic recoil of these vessels maintains blood flow and pressure during diastole. The second group, the muscular arteries, are the medium-sized vessels, such as brachial, radial, and femoral. In these vessels elastic tissue is present in smaller amount, and muscular tissue is greater. The third group, the arterioles, includes the small arteries of organs down to the size of capillaries. In these vessels muscular tissue is most abundant and elastic tissue relatively slight. Their contraction is important in regulation of blood pressure and flow.

Arteriosclerosis

Arteriosclerosis refers to a condition of hardening and thickening of arteries. Several types of change are included under this term, called atherosclerosis, medial sclerosis, and arteriolar sclerosis, affecting respectively the elastic, muscular, and arteriolar groups of vessels. In the first instance the change is in the intima, in the second type in the media, while arteriolar sclerosis may involve intima, media, or both. A fourth type, known as endarteritis obliterans, is a proliferative intimal change of small arteries.

Atherosclerosis.—Intimal thickening and degeneration are the characteristic features of atherosclerosis. It affects mainly the large elastic vessels, the aorta being most severely involved. It also affects the coronary and renal vessels, the arteries at the base of the brain, and larger vessels of the extremities.

The earliest change in the aorta is seen in the form of slightly raised, longitudinal, yellowish "fatty streaks." These are due to macrophages loaded with lipoid and some increased connective tissue in the intima. Further intimal thickening follows and irregular nodules of connective tissue develop around the fatty deposits, forming bluish-white translucent areas. The fatty deposits have the same lipid composition as the blood plasma, suggesting that there is a nonselective deposition of plasma lipids.⁴ Leary⁷ has de-

scribed a defense mechanism by which cholesterol deposits in arteries may be removed in early stages by lipolytic activity of fibroblasts.

The central portion of the nodular area of intimal thickening contains soft yellowish lipid substance and degenerated material. This lesion is an atheroma. The soft central mass is rich in lipoids, mainly cholesterol esters and crystals. The cholesterol crystals dissolve out in preparation of sections leaving elongated fusiform clefts. Calcium salts become deposited in the fatty areas and form thin, brittle, calcified plates. These crack easily, allowing escape of the necrotic atheromatous material and leaving an irregular area of ulceration. Thrombi are likely to form on such areas of intimal ulceration and rarely may occlude the lumen or give rise to emboli. The media is but little changed in this type of sclerosis, although some calcification of the media has been shown to precede the formation of the intimal patch.³

The aorta shows atheromatous changes in most marked degree, the lower abdominal portion usually being most severely involved. In the aorta, atherosclerosis produces but little narrowing of the lumen. The slight deleterious effects are due to rigidity of the wall and the occasional development of thrombi. Progressive loss of elasticity of the aorta occurs with advancing age but is not directly related to the atherosclerosis. Loss of aortic elasticity may be as great in the individual with slight atherosclerosis as with marked atherosclerosis.

In smaller arteries, such as coronary and cerebral vessels, atherosclerosis narrows the lumen and predisposes to thrombosis. Atherosclerosis of a renal artery may produce ischemia of the kidney and result in hypertension.

Medial Sclerosis (Mönckeberg's Sclerosis).—Medial sclerosis occurs particularly in the medium-sized muscular arteries. There are degeneration, swelling, and fragmentation of medial muscle fibers, followed by calcium deposition. Occasionally bone is formed in the vessel wall, the formation of osteoid tissue preceding calcification.⁹ The vessels become hard and tortuous, so that palpable vessels such as the radial can be felt as rigid tubes. The medial changes alone do not narrow the lumen and have little effect on the circulation. However, in the smaller vessels of the lower extremities, the medial sclerosis is frequently associated with intimal thickening due to proliferation and fatty deposits. This change, similar to that of atherosclerosis, decreases the circulation to the extremities so that nourishment is insuffi-

cient for active exercise, and finally even for the tissues when at rest. More important, however, is occlusion of the vessels by thrombosis⁹ and organization of the obstructing clots. The tissues with blood supply insufficient to maintain life became gangrenous. These changes are common in elderly individuals, but in diabetics they tend to occur in severe form and at an earlier age.

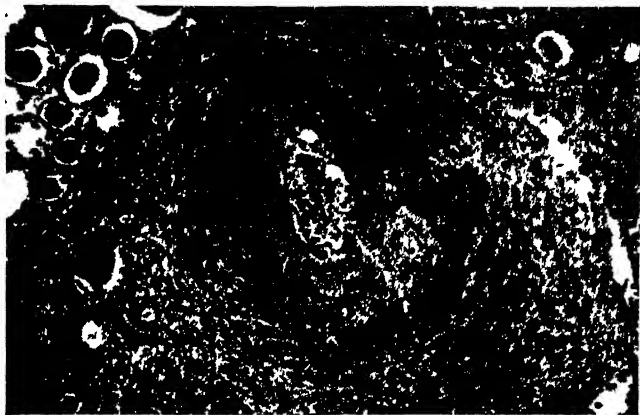


Fig. 83.—Endarteritis obliterans. Note the irregular thickening of the intima internal to the wavy and irregular dark line of the internal elastic lamina.

Endarteritis Obliterans.—Endarteritis obliterans refers to a localized obliterating process affecting small arteries. The wall becomes greatly thickened and the lumen narrowed or obliterated by marked overgrowth of connective tissue inside the internal elastic lamella. This intimal proliferative thickening is seen in small arteries in areas of chronic inflammation, e.g., adjacent to tuberculous cavities of the lung, or in the base of a peptic ulcer. It also develops in the blood vessels of a region where active circulation is no longer needed, i.e., as an involutionary change in vessels whose capillary beds have been reduced by tissue atrophy. Hence it occurs in the hypogastric arteries and ductus arteriosus after birth, in the arteries of the uterus and ovaries in old age, and in the involution of uterine arteries after pregnancy.

Arteriolar Sclerosis.—In arteriolar sclerosis of small arteries and precapillary vessels there are three main types of histologic change:⁵ (1) intimal hyalinization; (2) medial hy-

pertrophy and degeneration; and (3) intimal proliferation. These may occur separately or in combination. Intimal hyalinization is essentially a degenerative change which becomes more widespread and severe with advancing age. Medial hypertrophy is apparently the result of stretching,

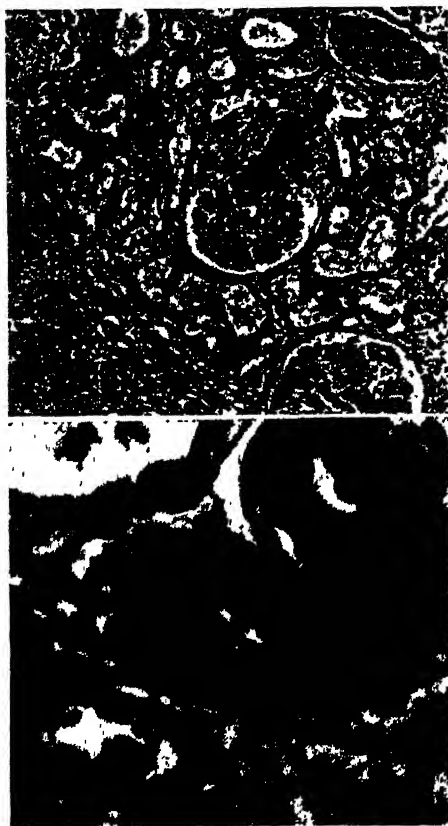


Fig. 84.—Hyaline arteriolar sclerosis of kidney. Note the severe involvement of the entering arteriole of a glomerulus. From a case of malignant hypertension.

and so is frequently associated with hypertension. The intimal proliferation is an endothelial hyperplasia with increase in elastic tissue, but secondary degenerative changes are common. This type of change is similar to that of endarteritis obliterans and may be associated with inflamma-

tory or adaptive change in the reduced circulation to an atrophic tissue.

Arteriolar sclerosis is commonly a widespread change but is seen particularly well in the spleen, pancreas, adrenal capsules, and kidney. In the kidney, but not necessarily elsewhere, arteriolar sclerosis is almost invariably associated with hypertension. Renal arteriolar sclerosis resulting in renal ischemia is possibly the mechanism of development of most cases of essential hypertension.

Etiology of Arteriosclerosis.—The etiology of arteriosclerosis is not known. Various causes operate in the different types of vascular change, and multiple factors come into play.⁶ Etiologic factors believed important are age, dietary and metabolic disturbances of cholesterol metabolism, hypertension, infection, inflammation, and injuries to vasa vasorum.

AGE.—Some vascular changes inevitably accompany the wear and tear of life and the aging of tissues. Certain types of arteriosclerotic changes, such as hyalinization of small arteries of the spleen and calcification of the media of the aorta,³ seem correlated with age. Most types of sclerosis, however, do not necessarily and constantly accompany advancing age.

CHOLESTEROL METABOLISM.—Diets high in cholesterol are effective in producing atherosclerotic lesions in rabbits. It has not been proved that high cholesterol intake or disturbances of cholesterol metabolism are of primary importance in causing human atherosclerosis, though such is not improbable.⁷ While hypercholesterolemia may promote the development of atherosclerosis, the latter commonly occurs in adults without obvious elevation of blood cholesterol or other abnormality of blood lipids.⁴

HYPERTENSION.—In the association of hypertension and arteriosclerosis, it is probable that the primary change is an arteriolar sclerosis affecting renal vessels, the resulting renal ischemia causing hypertension. The high blood pressure in turn apparently results in certain types of vascular change, e.g., medial hypertrophy of arterioles. Hence a vicious cycle tends to be established.

INFECTION AND INFLAMMATION.—Local injury of the vessel wall due to infection or inflammation may be an initial event in arteriosclerosis followed by lipid deposit. It has not been demonstrated that infection is of much importance in the causation of arteriosclerosis. Injury to small vessels by irradiation has caused development of small intimal plaques of foam cells,⁸ resembling the early stage of atherosclerosis.

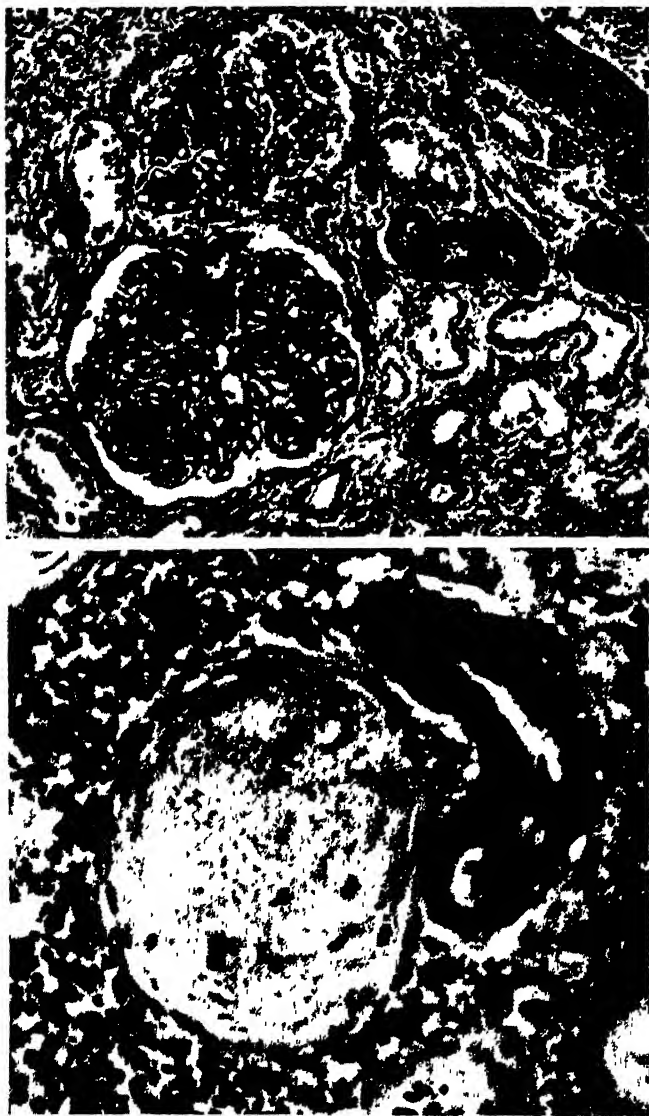


Fig. 85.—Arteriolar nephrosclerosis. From a case of severe hypertension. Note the thickening and prominence of the arteriolar walls.

INJURY TO VASA VASORUM.—Stern² points to occlusion and inflammation of the vasa vasorum as a possible initial injury leading to development of arteriosclerosis. Winternitz¹ has given evidence that abundant vasa vasorum may be found in all coats of the vessel wall and has suggested inflammatory exudate and hemorrhage from these vessels as an initiating event in arteriosclerosis. Patterson³⁹ and others believe that intimal vascularization and hemorrhage are a result rather than a cause of arteriosclerosis.

Inflammation of Arteries

Arteritis may be due to local inflammations which spread to involve vessel walls. There also occur primary forms of arterial inflammation, both localized and general. One of these primary forms is commonly called polyarteritis nodosa.

Polyarteritis Nodosa.—Polyarteritis nodosa (periarteritis nodosa) is an acute inflammation with degeneration and necrosis involving the walls of medium-sized and small arteries. Various organs and tissues may be involved, but most frequently the kidneys, heart, liver, gastrointestinal tract, and muscles. These tissues may be involved together or successively. The variety of organ involvement produces clinical pictures which are of great variability and difficult to diagnose. Biopsy of a nodule from skin or muscle frequently enables clinical recognition. The condition may occur at any age. It is estimated that about 10 per cent of cases recover.

The etiology has been variously ascribed to a specific virus, rheumatic fever, streptococci, and allergy. Frequent association of the condition with asthma or other allergic states and similarity to vascular changes in known allergic reactions favor the hypothesis that it may be a severe allergic manifestation.^{10, 11, 18}

The inflammatory changes have been thought in some instances to begin in the adventitia, and in other cases in the intima or innermost part of the media. Acute, subacute, chronic, and healed stages have been described. The earliest, or acute, phase is characterized by necrosis, usually of the media. In the subacute stage there is cellular exudation. Eosinophiles are the most characteristic cells of the inflammatory reaction, but lymphocytes, plasma cells, and polymorphonuclear leucocytes may be present. Exudation is followed by proliferative changes around the vessel, and also of the intima. Occlusion of the lumen and infarction are

common results. In the chronic phase granulation tissue develops and healing begins. Absorption of exudate and fibrosis result in the final healed condition. When various organs are involved successively, the several stages may be evident in the different organs.

Yellowish-red nodules which occur on the affected vessels are usually due to small localized dilatations or aneurysms at points of degeneration, inflammation, and weakening of the vessel wall. Nodules may be formed also by the localized cellular infiltration and proliferation. Rupture of one of the aneurysmal nodules may result in serious hemorrhage.

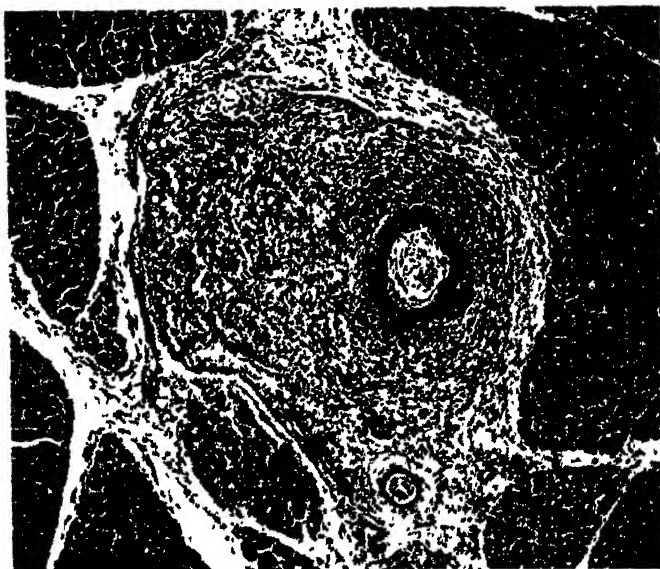


Fig. 86.—Periarteritis nodosa of pancreas.

Thromboangiitis Obliterans.—Buerger introduced the term thromboangiitis obliterans to describe an inflammatory condition of the vessels of the lower extremities in which thrombosis and later fibrosis interfere with the blood supply to the limbs. The condition occurs predominantly but not exclusively in males of the Jewish race and of Russian or Polish origin. The etiology is uncertain. By some it has been considered a specific infection, and others believe that allergy to tobacco plays an important role.

In the early stage an acute inflammatory reaction involves all coats of a segment of a deep artery and adjacent vein. Inflammatory thrombosis results. The process proceeds to a proliferative stage with organization and healing by fibrosis. Usually arteries, veins, and nerves become bound together in a dense fibrous scar. Some recanalization of the lumen often develops. Venous valves are damaged and disrupted by the inflammation and organization of thrombi. The early acute phase may give little clinical evidence of its presence. Following thrombosis and organization, insufficient



Fig. 87.—Buerger's disease. Fibrosis around arteries, veins, and nerve, with thrombotic obliteration of lumens. (From Berman, J. K.: *Synopsis of the Principles of Surgery*, The C. V. Mosby Co.)

blood supply to the extremity may result in pain on exercise (intermittent claudication) or even gangrene of the ischemic tissues. The degree of circulatory disturbance is largely influenced by the amount of collateral circulation which can be established.

Aneurysm

An aneurysm is a localized dilatation of an artery. The dilatation may be saccular, fusiform, or cylindrical. Certain

lesions, called false aneurysm, arteriovenous aneurysm, and dissecting aneurysm, are not true aneurysms in the sense of the above definition.

Syphilitic aneurysm, a late manifestation of syphilis, usually involves the first portion or the arch of the aorta, though the abdominal aorta or other vessels are occasionally affected. The localized dilatation is due to weakening of the media by destruction of the elastic tissue. Disruption and loss of elastic fibers are evident microscopically in the wall of the aneurysm. The media of the vessel is atrophic and replaced by connective tissue. The saccular variety is most common. It increases progressively in size, causing atrophy and erosion of any structure on which it impinges, including bony



Fig. 88.—Saccular aneurysm of aorta obstructing renal artery. Note the laminated thrombus in the aneurysmal sac, atrophy of the right kidney and hypertrophy of the left. The aortic intima above the aneurysm shows the characteristic "tree-bark" roughening of syphilitic aortitis. (Courtesy Dr. H. C. Schmeisser.)

tissue. Thrombosis in successive layers occurs in the aneurysmal sac. This serves to strengthen the wall to some extent, although there is but little organization of the thrombus. Aneurysms have little direct effect upon the heart or circulation, and symptoms are usually due to the pressure and erosion of adjacent structures. The final result is commonly perforation and death from hemorrhage.

Grossly similar aneurysms may arise as a result of atherosclerosis when its severity is sufficient to produce the re-

quired atrophy and weakening of the media. Such **arteriosclerotic aneurysms** are rare.

Aneurysms may occur in small arteries in which localized inflammation has produced sufficient weakening of the vessel wall. Such a process produces nodules in **polyarteritis nodosa**. In **mycotic aneurysm** the inflammation is due to the lodgment of an infected embolus, or infection of the wall by way of *vasa vasorum*. Occasionally extension of infection from inflamed aortic valves affects the sinuses of Valsalva or adjacent portions of the aorta, producing mycotic aneurysm in that area.



Fig. 89.—Syphilitic aortitis with beginning aneurysm. Elastic tissue (stained black) of the media destroyed in a local area, with bulging at the weakened point.

Congenital aneurysms occur particularly on superficial cerebral vessels, sometimes in miliary fashion. They are due to a muscular defect in the media at points of bifurcation, a small saccular aneurysm developing in the angle. In addition to the muscular defect, degeneration of the internal elastic membrane due to continued overstretching from blood pressure is necessary before aneurysm develops. The muscular defect, and not the aneurysm itself, is congenital. Rupture of such an aneurysm is an important cause of subarachnoid hemorrhage.

False aneurysm is an organized hematoma which communicates with the lumen of a blood vessel—i.e., the wall of the aneurysm is not composed of elements of the blood vessel wall. It occasionally follows a traumatic rupture of a small vessel, as by a knife or bullet.

Arteriovenous aneurysm is an abnormal communication between an artery and a vein. Its usual cause is traumatic

penetration of an adjacent artery and vein. Less commonly, it may be a developmental anomaly, or occur in vascular neoplasms (glomus tumor). The vessels may communicate through a short passage which is really a false aneurysm. If vessels of considerable size are involved, the direct arteriovenous shunt produces disturbed circulation. Congestion and increase of blood pressure are present in parts distal to the aneurysm. Cardiac hypertrophy may result from the increased load.

Dissecting aneurysm is produced by penetration of circulating blood into the wall of a vessel and its subsequent extension for varying distances between the layers. The aorta is the vessel commonly involved. It is simply a hemorrhage into the vessel wall itself, which by its force splits or "dissects" the layers of the wall.

The dissection is through the media of the vessel and extends for short or long distances proximally or distally. At the end of its dissection it may rupture externally by tearing through the outer portion of the wall. Less commonly it perforates again into the lumen. Sudden death results from perforation externally into surrounding tissues, or into the pericardial sac (producing cardiac tamponade) when the first portion of aorta is involved. Rupture back into the lumen occasionally leads to recovery, either through lining of the channel by endothelium, or more rarely by thrombosis, organization, and fibrous obliteration of the channel.

About 70 per cent of dissecting aneurysms begin in the ascending aorta. The intimal tear at this point is usually transverse, irregular, and one or two cm. in length. Dissection distal to the primary tear is longer and more important than that proximal to the rupture, though some proximal dissection almost always occurs. Since a large proportion of primary tears are one or two cm. above the aortic valve, the frequency of rupture into the pericardial sac is easily understood. Dissection distally may progress to the aortic bifurcation and beyond.

The underlying cause of dissecting aneurysm is some degenerative change or defect of the media. Shennan¹⁸ has described the medial changes as a fatty degeneration and atrophy of muscle fibers; hyaline and mucoid degeneration of connective tissue; swelling, fragmentation, and loss of staining power of elastic fibers. Peculiar areas of necrosis and mucoid degeneration are found in the media (**medionecrosis aortae idiopathica cystica**). These degenerative changes are without inflammatory reaction, but associated

with necrosis and small cystlike spaces between the elastic fibers. Syphilis is not an etiologic factor in dissecting aneurysm. One-fourth of cases occur before the age of 40 years, and sometimes with pregnancy.

The exciting cause is usually (according to Shennan) a sudden increase of blood pressure due to mental or physical stress; trauma is rarely a factor. The primary tear of the intima may start at an atheromatous ulcer, but this is unusual. In some cases the primary hemorrhage may be from one of the vasa vasorum, and the intimal tear secondary to this.

Phlebitis

Inflammation of veins is often extension of a local infection to involve their walls. Such an event is common in the infected puerperal uterus, or as a complication of appendicitis (pylephlebitis). Thrombosis usually develops in the infected veins, and spread of the infection may thus occur by infected emboli as well as directly along the vein wall. Phlebitis occasionally complicates acute infectious diseases.

Varicose Veins

Abnormally distended or varicose veins are produced by increased intravenous pressure, and weakness of the vein walls, alone or in combination. The condition is seen most frequently in the veins of the lower extremities, the hemorrhoidal veins, or the veins at the lower end of the esophagus.

Varicose veins of the lower extremities interfere with proper circulation and nourishment of the tissues, so that atrophy and ulceration of the skin may result. Lack of certain valves in large veins of the extremities²³ and an obstructive anomaly of the opening of the left common iliac vein²⁴ have been pointed out as possible contributing etiologic factors.

Hemorrhoids are varicosities of hemorrhoidal veins. Varices at the lower end of the esophagus are common where there is obstruction in the portal circulation, as in cirrhosis of the liver. Rupture of one of these distended vessels is a common terminal event in cirrhosis of the liver.

Lymphangitis

Inflammation of lymphatics may appear in infections, and spread may occur from a local area along lymphatics to lymph nodes. When such inflammation is superficial, e.g.,

on the arm, the lymphatic involvement may be seen as reddish, painful streaks, and the lymph nodes of the axilla become enlarged and tender (lymphadenitis, see page 419).

Lymphatic Obstruction

Obstruction of lymphatic flow from an area results in retention of fluid in the part, which becomes enlarged and hard. Marked degrees of the enlargement are termed elephantiasis and are most common when the lymphatic obstruction is due to filaria, though a similar effect is produced by inflammatory destruction of lymphatics. Operative procedures may interfere with normal lymph drainage, and in the case of radical amputation of the breast, an enlargement and brawny edema of the arm may result.

Tumors of Blood and Lymphatic Vessels

Angiomas are tumors made up of blood or lymph vessels (hemangioma or lymphangioma). They are often congenital and probably arise from embryonic rests of mesodermal tis-

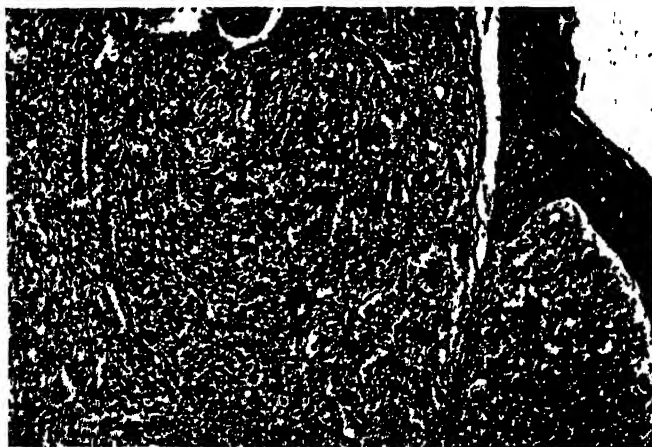


Fig. 90.—Hemangioma of skin. The squamous epithelial surface is evident on the right. The tumor is composed of tiny, thin-walled blood channels and proliferating endothelial cells.

sue. Some may be simply vascular malformations, but many are true neoplasms. Angiomas are common in childhood.

Hemangioma.—There are several types of hemangiomas. **Capillary hemangioma** is composed of well-differentiated,

thin-walled capillaries. **Cavernous hemangioma**, in which the vascular spaces are dilated, engorged blood sinuses, is the common type in internal organs, such as the liver. **Nevus venosus** (port wine stain) is a diffuse telangiectasis or dilatation of superficial vessels of an area of skin, usually of the face or neck. **Hemiangioendothelioma** consists of solid masses of proliferating endothelial cells, with only a few patent vessels. This type is locally invasive in its growth, and prone to recur after treatment. **Sclerosing hemangioma** is a blood vessel tumor in which there is overgrowth of the collagenous connective tissue framework of the tumor. This results in occlusion of the vessels and breakdown of trapped red cells. Phagocytes containing hemosiderin pigment may be sufficiently numerous to give the tissue a brownish color. Other macrophages contain lipid material. A few giant cells are usually present. The tumor must be differentiated from a melanoma or a xanthoma.



Fig. 91.—Glomus tumor.

Lymphangioma.—The three main types of lymphangioma are the simple or **capillary**, the **cavernous**, and the **cystic (hygroma)**. The capillary and cavernous types are similar to the corresponding hemangiomatous tumors, but differ in the absence of red cells in their channels and in the frequent presence of lymph follicles and lymphocytes.

The cystic type of lymphangioma or hygroma occurs in the neck or axilla, designated respectively as **hygroma colli**

cysticum and **hygroma axillare**. Originating from lymphatic nests, which retain embryonic power of irregular growth, they grow to be large, multilocular cystic tumors. Their cavities are lined by endothelium and contain straw-colored fluid. Lymphoid tissue is often abundant in the cyst walls.

Glomus Tumor (Angiomyoneuroma).—The glomus is an arteriovenous anastomosis, found normally in the skin and concerned with temperature regulation. The glomus tumor, or angiomyoneuroma, arising from this structure occurs in the extremities and is characterized clinically by intense pain and tenderness. Vasomotor phenomena and atrophic changes in the involved extremity are sometimes associated.

The tumors are composed of a tangled mass of blood vessels enclosed within a capsule. In the vessel walls are masses of peculiar cuboid or rounded "glomus" cells, probably derived from pericytes, and smooth muscle cells. Bundles of myelinated nerves are recognizable in or near the capsule of the tumor, from which slender, nonmyelinated fibers pass among the "glomus" cells and become continuous with their cytoplasm.



Fig. 92.—Cystic hygroma of the neck. (Courtesy Dr. H. C. Schmeisser.)

Hemangiopericytoma.—Stout and associates²⁰ have described a vascular tumor composed of endothelial tubes surrounded by rounded or elongated cells which they believe are derived from pericytes, as are the epithelioid cells of the glomus tumor. Pericytes, described by Zimmerman, are contractile cells wrapped about capillaries, which function in changing their lumens. Most examples have been benign, but local invasion and even metastases have been reported.

DISEASES OF THE HEART

Congenital Heart Disease

Congenital malformations of the heart are usually either (1) abnormalities of the great vessels or their valves: (2)

failure of completion of the septa between auricles or ventricles; or (3) anomalies of size or position of the heart. Frequently two or more anomalies occur in association. Defects which cause a shunt of blood from the venous to the



Fig. 93.—Coarctation of aorta. (Courtesy Dr. V. Moragues.)

arterial side (i.e., from right to left) are commonly associated with cyanosis. The main factor in the cyanosis is the admixture of venous and arterial blood in the peripheral circulation. The oxygen deficiency gives rise to a compensa-

tory increase in number of red cells in the blood (polycythemia) and increase in their average size. Clubbing of the ends of fingers and toes is also common in such cases.



Fig. 94.—Congenital defect of interventricular septum (ostium atrio-ventriculare commune). (Courtesy Dr. V. Moragues.)

Pulmonary Stenosis.—Narrowing of the opening of the pulmonary artery is a common and important anomaly. In most cases it is associated with a defect of the interventricular septum, patent foramen ovale, or patent ductus arteriosus. The right ventricle becomes hypertrophic.

Patent Ductus Arteriosus.—Normally during fetal life, blood passes from the pulmonary artery through the ductus

arteriosus to the aorta, thus by-passing the lungs. Obliteration of the channel occurs a few weeks after birth. When it remains open, it is often associated with other defects, such as pulmonary stenosis or patent septa.

Aortic Stenosis and Coarctation of the Aorta.—Narrowing of the aortic valve opening is less common than pulmonary stenosis. Narrowing of the aorta beyond the valve (coarctation of the aorta) occurs in infantile and adult types. In the infantile type there is a narrowing of the aorta between the origin of the left subclavian artery and the insertion of the ductus arteriosus. This narrowing is an exaggeration of the normal fetal condition. In the adult type there is a sharp constriction of the aorta below the insertion of the ductus arteriosus. Compensatory collateral circulation develops through internal mammary and intercostal vessels, and the left ventricle hypertrophies.

Patent Interauricular Septum.—It is frequently found that the foramen ovale has remained open, but with a competent though unfused valve. In such cases no important transseptal leakage occurs. However, with a widely patent, inadequately guarded foramen ovale, a shunt of blood from left to right occurs, with enlargement of right auricle, right ventricle, and pulmonary artery. The left ventricle remains relatively small.

Patent Interventricular Septum.—Patency of the interventricular septum, usually in its upper membranous portion, is a common anomaly. Small defects may cause little disturbance. Large defects cause relative hypertrophy of the left ventricle and may be associated with cyanosis, dyspnea, polycythemia, and clubbing of fingers.

Tetralogy of Fallot.—The tetralogy of Fallot is a common association of defects which includes (1) a patent interventricular septum; (2) pulmonary stenosis; (3) relative displacement of the aorta to the right so that it tends to lie above the patent part of the interventricular septum; and (4) hypertrophy of the right ventricle with a relatively small left ventricle.

Lesions of the Pericardium

Abnormalities of the pericardium are usually secondary to diseases elsewhere, rarely primary.

Serous Atrophy of Pericardial Fat.—In any chronic disease with marked emaciation the subepicardial fat may be reduced in amount and acquires a watery, translucent gelatinous character.

Hydropericardium.—The pericardial sac normally contains about 30 to 50 c.c. of fluid. More than 100 c.c. is called hydropericardium, and amounts as large as one or two liters may accumulate. The usual cause is nephritis or cardiac failure. Large amounts present some interference with the heart's action and reduce inflow by pressure on incoming veins.



Fig. 95.—Hemopericardium. Due to rupture of aneurysm into pericardial sac. (Courtesy Dr. H. C. Schmeisser.)

Hemopericardium.—Petechial hemorrhages of the pericardium are common in many toxic, infectious and asphyxial conditions. Actual hemorrhage into the pericardial sac (hemopericardium) may result from cardiac rupture following infarction, rupture of a saccular or dissecting aneurysm of aorta into the pericardium, or penetrating wounds of the pericardium. The effect depends upon the rate of hemorrhage as well as on the amount. Acute hemorrhage with rapid accumulation in the sac of 200 or 300 c.c. may interfere with cardiac action and cause death (cardiac tampon-

ade). Slow leakage of a liter or more of blood into the sac may interfere less with the heart's action.

Acute Pericarditis.—Acute pericarditis may be caused by rheumatic fever, pyemia, certain infectious diseases and spread from adjacent inflammations of pleura, lung, mediastinum, and myocardium. Mild pericarditis is usual over myocardial infarctions, and sometimes occurs in uremia. The exudate may be fibrinous, serofibrinous, or purulent.



Fig. 96.—Acute fibrinous pericarditis. Note the shaggy coat of fibrin covering the surface of the heart. (Courtesy Dr. H. O. Schmeisser.)

When the exudate is predominantly fibrinous, movements of the heart form the fibrin into cords or villi, and the surface of the heart and parietal pericardium have a peculiarly shaggy appearance.



Fig. 97.—Tuberculous pericarditis. Note the tremendous thickening of visceral and parietal pericardium, the massive caseation of the mediastinal lymph nodes, and the tuberculous areas in lung tissue. (Courtesy Dr. H. C. Schmeisser.)

Tuberculous Pericarditis.—Tuberculous pericarditis is usually due to extension from adjacent lung, pleura, or mediastinal lymph nodes. It is a chronic serofibrinous pericarditis, characterized by very marked thickening of visceral and

parietal layers. A thick layer of tuberculous granulation tissue, with organization and healing often results in firm pericardial adhesions.



Fig. 98.—Adhesive pericarditis. The pericardial sac has been opened, and the fibrous bands joining visceral and parietal pericardium are evident. (Courtesy Dr. H. C. Schmeisser.)

Chronic Pericarditis and Pericardial Scars.—True chronic pericarditis is quite rare. More commonly seen are the scars or adhesions of a previous acute pericarditis. These scars are usually whitish irregular areas of fibrosis on the anterior surfaces of the ventricles and often called “soldier’s spots”

or "milk plaques." They represent areas of organized and scarred pericardial exudate.

Adhesions between visceral and parietal layers of pericardium may vary from just a few bands to complete obliteration of the sac. Adherent pericardium does not give rise to cardiac hypertrophy, but it does embarrass cardiac action and may lead to congestive cardiac failure.²⁷ Entering veins are constricted, and increased systemic venous pressure, ascites, and hydrothorax develop. Similar progressive hyaline thickening and adhesions may involve the serosa over the spleen, liver, and undersurface of the diaphragm (Pick's disease).

Rheumatic Fever

Rheumatic fever is a disease which seriously affects the heart and also involves arteries, joints, tendons, subcutaneous tissues, and the nervous system. It is usually acquired in childhood, and is widespread in temperate zones, but less common in warm climates. It is the chief cause of heart disease under 40 years of age.

The etiology is still unsolved. It is apparently a low-grade infection, in which hereditary susceptibility plays a part. Much evidence has indicated the importance of hemolytic streptococcal infections, though the relationship is evidently not a direct one. The leading explanations have been that rheumatic fever is a manifestation of allergy or hypersensitivity to hemolytic streptococci; that it is due to a filtrable virus; or to a virus acting in synergy with other infectious agents, particularly streptococci. Experimental cardiac lesions having basic similarities to those of rheumatic fever have resulted from anaphylactic hypersensitivity.²⁸

Characteristic lesions of rheumatic fever are innumerable minute foci of injury to interstitial and supporting tissues, i.e., collagen and elastica. The heart and blood vessels especially are susceptible, and cardiac involvement is particularly fatal. In certain acute phases the inflammatory reaction may be exudative, but the important change is a degenerative and proliferative type of reaction. In each tiny focus of injury there occurs a degenerative change in connective tissue, and proliferation of histiocytic cells, forming a "submiliary" granuloma. In their characteristic form, as may be seen in the myocardium, each of these minute nodules of proliferative inflammation is known as an Aschoff body. The eventual result is fibrosis.

Rheumatic Heart Disease.—Death may occur during the acute phase of rheumatic fever, but most deaths occur years



Fig. 99.—Aschoff bodies in the myocardium. Note the perivascular position in the upper figure, and the characteristic large dark cells.

after the acute attack and are due to valve deformities. The cardiac involvement is a pancarditis, i.e., pericardium, myocardium, and endocardium are injured. **Pericarditis** is important mainly in acute phases; it is frequently associated with inflammatory effusion. The **myocarditis** is characterized by the presence of Aschoff bodies, and the development of areas of fibrosis. The myocardial fibrosis is due in part to involvement of coronary vessels as well as to fibrous change in Aschoff nodules and results in a weakened heart muscle. The **endocarditis** very commonly leads to mitral stenosis, and often to aortic stenosis, but only occasionally affects the tricuspid valve. These serious valvular deformities along with myocardial involvement result in a failure of the circulation.



Fig. 100.—Rheumatic vegetations, mitral valve. (Courtesy Dr. V. Moragues.)

The **Aschoff body**, as it occurs in the myocardium, is an oval or elongated nodule of microscopic size, situated interstitially between muscle fibers, and often adjacent to a small blood vessel. Swelling, degeneration, and fragmentation of collagenous fibers and the presence of Aschoff cells are characteristic features. The Aschoff cells are large, elongated, and irregular, often with multiple vesicular nuclei, and granular basophilic cytoplasm. These proliferative cells are derived from histiocytes, or primitive resting mesenchymal cells. Lymphocytes, plasma cells, or even polymorpho-

nuclear leucocytes also may be present in acute phases. Gradual transformation of the Aschoff cells into fibroblasts results in a tiny fibrous scar in which lymphocytes may persist for many months.

Rheumatic lesions occurring elsewhere than in the myocardium are composed of the same elements, but less regularly arranged and of different shape and distribution, and hence they are less easily recognized.

RHEUMATIC ENDOCARDITIS.—The mitral valve is involved in practically all cases of rheumatic carditis, the aortic in one-half, and the tricuspid in one-third of the cases. The earliest changes are in the subendothelial layers, with degeneration of connective tissue and proliferative activity. The inflammation spreads throughout the whole valve substance, and histologically it shows edema, an exudate of macrophages, plasma cells and lymphocytes, with occasional neutrophiles, and formation of young capillaries. The endothelium is destroyed. Vegetations form at the line of contact of the leaflets (i.e., areas of trauma), usually 1 to 5 mm. from the free margin. These vegetations are multiple, firm, small, smooth, warty masses, which consist mainly of platelets and fibrin. Bacteria are absent. Being firm and not crumbly, they do not give rise to emboli. Areas of hyalinization and necrosis develop within the inflamed tissue. Healing of the inflammation results in a thick, distorted, retracted, and insufficient valve. Severe degrees of stenosis are a particularly common result in the mitral valve. Frequently the mural endocardium is also involved. The endocardium of the left auricle, just above the posterior leaflet of the mitral valve, is often thickened and irregular. The microscopic picture is similar to that seen in the valves. Chordae tendineae also are involved, and eventually become shortened and fibrous.

Extracardiac Rheumatic Lesions.—"Growing pains," a frequent minor manifestation of rheumatism in children, are due to synovitis of the hamstring tendons. Heel pain is due to synovitis of the bursa of the Achilles tendon. Torticollis (wryneck) illustrates involvement of muscles. Small subcutaneous nodules are often present and consist of degenerative and proliferative lesions, essentially similar to rheumatic lesions elsewhere.

In joint involvement (rheumatic polyarthritis) the synovial membranes are swollen and hyperemic. The increased fluid in the joint is cloudy but not purulent. Degenerative and necrotic changes and granulomatous formations are

present in deeper structures: these are similar to Aschoff bodies. Ankles, knees, and wrists are most often affected.

Involvement of the nervous system, clinically called Sydenham's chorea (Saint Vitus' dance), is a diffuse meningo-encephalitis which is rarely fatal. Aschoff bodies are not found in the nervous system, but one sees congestion and thrombosis of small vessels, endothelial proliferation, and perivascular round-cell infiltration.

Pleural involvement is very common in rheumatic fever. Rheumatic pleurisy is usually associated with effusion of sterile, serofibrinous fluid. Sometimes the exudate is highly fibrinous and heals with fibrous pleural adhesions. The lung may have characteristic rheumatic involvement of small blood vessels, but a specific rheumatic pneumonia has also been described (see p. 363).

Bacterial Endocarditis

Bacterial infections of endocardium, which are in reality involvements of cardiac valves, form two groups of conditions which differ in their bacterial etiology, pathogenesis, clinical effect, and pathologic anatomy. They are commonly called acute and subacute bacterial endocarditis. The acute variety usually runs a rapid course of less than six weeks.

Subacute Bacterial Endocarditis.—

ETIOLOGY AND PATHOGENESIS.—Subacute bacterial endocarditis (endocarditis lenta) is due to *Streptococcus viridans* in more than 95 per cent of cases, and in most of the remaining cases to the *B. influenzae*. The focus of infection from which the organisms reach the heart usually is not obvious. Bacteriemia is believed to occur by entrance of organisms from such foci as infected teeth or tonsils. Such mild and transient bacteriemias are probably quite common, and other factors are necessary for the localization of the organisms on the valves. Previous damage to a valve, certain congenital cardiac abnormalities, and platelet thrombi on the surface of valves are important predisposing factors. Subacute bacterial endocarditis is often superimposed on an old rheumatic valvular injury, or it affects congenitally bicuspid aortic valves.^{30, 31, 32} Patency of the ductus arteriosus also appears to predispose to endothelial infection.

The streptococci may gain a foothold on injured or deformed valves by infecting rheumatic vegetations, or by localizing in nonbacterial vegetations (degenerative verrucal endocardiosis) which have been found to occur in a variety

of conditions.^{30, 34} The valvular vegetation forms a suitable medium for the multiplication of the organisms. While the organisms are of low virulence, they are so protected in the vegetations against the body's natural defenses, or therapeutic agents, that the disease almost invariably pursues a slow relentless course to a fatal termination. Healing and recovery have been described only in rare cases, but penicillin therapy has given evidence of therapeutic effectiveness and justifies hope of cure in some cases.

CARDIAC LESIONS.—The tendency to affect injured valves has already been emphasized. The mitral is most commonly involved, and the aortic next in frequency, with tricuspid and pulmonary lesions relatively rare. Vegetations form on the valves as warty or polypoid friable masses, from which portions are easily detached. They are more friable and detachable than rheumatic vegetations, but are firmer and have less tendency to ulceration and valve destruction than the vegetations of acute endocarditis. The vegetations are prone to extend, so as to involve mural endocardium and chordae tendineae. From the mitral valve the vegetations may spread up on the left posterior wall of the auricle. This involvement of mural endocardium assists in differentiation from acute endocarditis. Microscopically, the vegetations consist of masses of necrotic tissue with some fibrin, platelets and leucocytes covered by a layer of bacteria, lying on granulation tissue and possessing a fibrous base which merges with underlying endocardium. Fibrin usually forms a protective mantle on the surface of the vegetation. Allen³⁵ has presented evidence that the bulk of the vegetations consists of degenerated and inflamed valvular tissue, rather than thrombotic material derived from blood.

Changes in the myocardium are usually slight and inconstant. In some cases there are minute abscess-like areas in the myocardium, called Bracht-Wächter bodies. Subpericardial hemorrhages are quite common.

EXTRACARDIAC LESIONS.—Pathologic changes in organs other than the heart result from breaking away of small portions of the friable valvular vegetations. The effects of embolism give rise to a varied symptomatology. Embolism is evidenced in the kidney by hematuria and focal nephritis, in the spleen by pain due to infarction, in the skin by petechiae, in the retina by hemorrhages and blindness, in the brain by hemiplegia or other evidences of cerebral infarction, and in blood vessels themselves by the formation of mycotic aneu-

rysms. Due to the low virulence of the organisms, a suppurative reaction is uncommon in the embolic lesions.

The renal lesion associated with subacute bacterial endocarditis (embolic glomerulonephritis) usually has definite peculiarities. The smooth surface of the slightly swollen kidney is covered by punctate hemorrhages, so that they have been called "flea-bitten kidneys." Microscopically, the focal nature of the change is characteristic; only certain glomeruli are involved, and the rest are normal.

While bacteriemia is usually demonstrable throughout the disease and is a useful feature in diagnosis, bacteria-free periods may occur, even though there are repeated emboli to various organs.



Fig. 101.—Pneumococcal endocarditis. Large vegetations on the mitral valve.

Acute Bacterial Endocarditis.—Acute bacterial endocarditis (ulcerative endocarditis) may be caused by the *Streptococcus hemolyticus*, *pneumococcus*, *Staphylococcus aureus*, *gonococcus*, or rarely by other organisms. The endocarditis and septicemia, while rapidly fatal, are often but a complication of another serious condition, such as lobar pneumonia. Thus, unlike the subacute form, the primary focus of the infection is usually obvious.

The mitral and aortic valves are most commonly affected, except in gonococcal infection which often involves the right side of the heart. The vegetations on the valves tend to be dense, large, friable, and with a tendency to ulceration and destruction of the valve. Actual perforation of a valve may occur. Spread to involve mural endocardium is less frequent

than in the subacute type of endocarditis. The vegetations consist of an outer layer of fibrin, beneath which is a densely staining mass of bacteria. Deeper zones are composed successively of leucocytes, granulation tissue, and fibrous connective tissue. The embolic lesions, which are often numerous, tend to be suppurative. The termination, particularly in pneumococcal endocarditis, is often in purulent meningitis.

Atypical Verrucous Endocarditis (Libman-Sacks).—Warty mural and valvular vegetations, which represent neither the rheumatic nor bacterial types of endocarditis, have been described by Libman and Sacks. It is frequently associated with disseminated lupus erythematosus³⁵ (see p. 642).

Valvular Deformities

Deformities of cardiac valves result from a healed or chronic valvulitis, or occasionally are congenital malformations. The results of inflammation in the valves are seen as thickening, adhesions, retraction, and shortening of the leaflets. There may be a narrowing of the valve opening (stenosis) or closure of the valve may be insufficient, so that leakage (regurgitation) occurs through it. Valvular insufficiency and stenosis may be produced by the same deformity. Valve deformities are common on the left side of the heart (aortic, mitral) but rare on the right side (tricuspid, pulmonary).

Aortic Stenosis.—Uncomplicated aortic stenosis is rare, but some stenosis may accompany the valvular changes causing regurgitation. The valve leaflets are thickened, nodular, adherent, and often calcified. The change is most commonly rheumatic. The effect is to increase greatly the work of the left ventricle, which undergoes hypertrophy.

Aortic Insufficiency.—Regurgitation through the aortic valve during diastole may result from dilatation of the aortic ring, or changes in the leaflets themselves. Dilatation of the ring may accompany dilatation of the rest of the heart, or it may be due to spread of syphilitic aortitis. Changes in the leaflets are commonly due to syphilis or rheumatism. The leaflets may be simply adherent and flattened at the commissures, but often the whole leaflet is thickened, with rounded edges, and marked shortening and retraction. Diastolic regurgitation through the aortic valve is accompanied by marked fall of systemic diastolic pressure and hence a high pulse pressure. Marked hypertrophy of the left ventricle results from the extra work.

Mitral Stenosis.—Mitral stenosis is one of the commonest valve deformities and almost invariably is due to rheumatic inflammation. Thickening, adhesions, and retraction of valve leaflets and chordae tendineae may produce all degrees of stenosis. The orifice may be narrowed to a tiny slit or "button-hole." The rigidity and retraction usually cause some insufficiency of the valve as well.

Increased work of the left auricle will compensate for a mild mitral stenosis. A more severe uncompensated stenosis results in increased pressure and stasis in the pulmonary circulation and increases the work of the right ventricle. Thus, left auricular dilatation, chronic passive congestion of the lungs, and right ventricular hypertrophy constantly accompany any marked degree of mitral stenosis.



Fig. 102.—Mitral stenosis. Button-hole valve opening.

Mitral Insufficiency.—Regurgitation through the mitral valve is most often a relative insufficiency due to dilatation of the mitral ring accompanying a dilatation of the left ventricle. But insufficiency also may be due to shortening and retraction of the leaflets and chordae tendineae. If regurgitation is severe, one finds auricular dilatation, marked hypertrophy of the right ventricle, and moderate hypertrophy of the left ventricle.

Tricuspid Stenosis.—Tricuspid stenosis is rare but may result from rheumatic inflammation.

Tricuspid Insufficiency.—Tricuspid insufficiency is usually due to dilatation of the right heart, with associated dilatation of the valve ring.

Pulmonary Stenosis.—Pulmonary stenosis is due to congenital deformity of the ring, rather than inflammatory scarring. It results in right ventricular hypertrophy.

Pulmonary Insufficiency.—Leakage through the pulmonary valve is very rare. It is usually due to dilatation of the right side of the heart.

Heart Block

The rate and rhythm of contraction of the heart are controlled by a specialized muscular mechanism consisting of the sinoauricular node (Keith-Flack), the auriculoventricular node (Tawara), and the auriculoventricular bundle, which divides into right and left bundle branches going to the respective ventricles.

The sinoauricular node, "the pacemaker," is situated beneath epicardium just below the entrance of the superior vena cava. The auriculoventricular node lies at the base of the interauricular septum, between the orifice of the coronary sinus and the membranous portion of the septum. This node is continued as the auriculoventricular bundle, which runs obliquely downward to the lower edge of the membranous portion of the interventricular septum, where it divides into right and left branches which proceed to the apices of the right and left ventricles. The blood supply of the auriculoventricular node and bundle and of a posterior division of the left bundle branch is from a branch of the right coronary. The right bundle branch and the anterior division of the left branch are supplied by vessels from the anterior descending division of the left coronary.

Lesions involving these specialized conducting tissues produce partial or complete heart block, i.e., an interference with the proper conduction of impulses manifested by disturbances in the cardiac rhythm. Yater³⁸ has studied the lesions associated with bundle branch block and finds that they are usually scars due to coronary artery disease or to rheumatic fever. The more common left bundle branch block is usually found with coronary sclerosis or in hypertensive hearts, while the rarer right bundle branch lesions are often the result of rheumatism. Usually both bundle

branches are affected, but one more seriously than the other. Gumma in the upper part of the interventricular septum is a rare cause of destruction of conducting tissue.

Coronary Disease of the Heart

The Coronary Circulation.—Right and left coronary arteries supply the heart, taking their origin from a protected position in the aortic sinuses of Valsalva. Tiny accessory openings occasionally occur adjacent to the main openings. The right coronary curves to the right in the auriculoventricular groove as the right circumflex artery, and then descends in the posterior interventricular sulcus as the posterior descending branch. The right coronary supplies the posterior half of the interventricular septum, a portion of the posterior part of the wall of the left ventricle, two-thirds of the anterior portion of the right ventricle, and the right auricle. The left coronary early divides into circumflex and anterior descending branches. The circumflex branch supplies the left auricle and the left margin of the left ventricle. The anterior descending branch of the left coronary runs toward the apex in the anterior interventricular sulcus and supplies the anterior wall of the left ventricle, the left third of the anterior wall of the right ventricle, and the anterior half of the interventricular septum.

In normal hearts anastomotic communications between coronary vessels are small, less than 40 microns in diameter, and these are probably of little functional significance.⁸⁷ However, when the coronary supply is interfered with by arteriosclerotic narrowing or occlusion, anastomotic channels develop and enlarge where needed, and they may measure as much as 200 microns. Such anastomotic development may do much to compensate for arteriosclerotic changes.

The thebesian veins are minute channels which open directly into the cardiac chambers. Under abnormal circumstances, flow in these channels may be reversed, and they may assist in nutrition of myocardium. Most of them open into the auricles, and more than 90 per cent are on the right side of the heart. Their assistance possibly contributes to the comparative rarity of infarction of the muscle of atria or right ventricle, although the more direct course of branches supplying the right ventricle also may be a factor.

Coronary Sclerosis.—Arteriosclerosis involving coronary vessels is of the atherosclerotic intimal type (see p. 229). Intimal fibrous thickening, lipid deposits, and often calcium

deposition, all of which narrow the lumen of the vessel, are the main features. The larger vessels on or near the surface of the heart are particularly involved. Small arteries within the myocardium rarely show any marked sclerosis. The left coronary is usually more severely affected than the right.

The intima of normal coronary arteries is without demonstrable vasa vasorum, but in and around atherosclerotic lesions may be found capillaries, some of which take their origin from the lumen of the artery. The importance of hemorrhage from these delicate channels in the initiation of coronary thrombosis has been emphasized by Paterson.^{3a}

The etiology of coronary arteriosclerosis is obscure. Heredity, sex, and race are factors of importance. In women of young and middle ages coronary disease is seldom severe. Also in American Negroes, coronary arteriosclerosis is relatively mild. Hypertension appears to have no direct relationship to coronary disease and the two conditions may or may not be found together.

Coronary arteriosclerosis, by decrease of blood supply to the myocardium, causes ischemic degeneration and necrosis. Patchy areas of fibrous scarring develop throughout the myocardium. Similar scars may be produced by infectious diseases, toxins, or rheumatic fever, but in a great majority of cases, myocardial fibrosis is the result of coronary disease. When narrowing of coronary vessels or rigidity of their walls progresses to the point that coronary circulation is insufficient for the heart during periods of increased work, myocardial anoxemia results, and the individual may suffer the pain of angina pectoris. Such coronary insufficiency results in myocardial damage, and when the insufficiency is severe, the acute myocardial damage may resemble an infarct.

Myocardial fibrosis is often evident on the cut surface of the myocardium in the form of tiny, translucent, grayish-white patches which contrast with the brown color of the muscle. In microscopic preparations the small irregular areas of fibrosis are more readily seen. The heart shows no marked hypertrophy unless complicated by some other condition, such as hypertension.

The effects of coronary sclerosis and myocardial fibrosis vary with their degree. Milder forms simply decrease the cardiac reserve, so that increased work by the heart, as from exercise, may cause dyspnea or cardiac pain (angina pectoris). With severe degrees of coronary disease, the heart

may fail to meet the demands of the body even at rest, so that congestive circulatory failure results. The severest myocardial fibrosis is usually found in those patients who have finally developed congestive failure.

Coronary Occlusion.—Complete blockage of a coronary lumen may result from (1) thrombosis, (2) progression of the arteriosclerotic process, (3) syphilis about the coronary openings, and (4) embolism. Most coronary occlusions are within 3 cm. of the openings of these vessels. Depending upon the location of the occlusion, the degree of anastomotic circulation available, and other factors, the result may be one of (1) sudden death, (2) myocardial infarction with

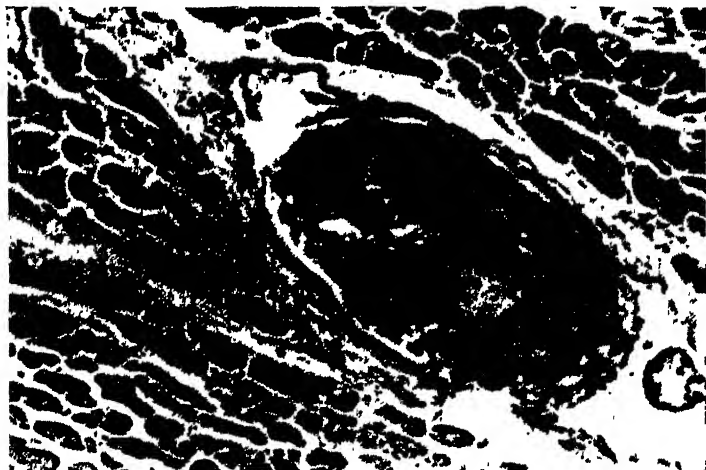


Fig. 103.—Thrombus in small intramural coronary vessel.

sequelae, or (3) simply additional myocardial scarring without clinical evidence of occurrence of the occlusion. Demonstration of coronary occlusion at autopsy is most accurately accomplished by a roentgenographic picture of the heart following injection of radiopaque material into the coronaries.^{37, 40} The coronary arteries should be opened by cutting the vessels transversely at frequent intervals. Longitudinal slitting may displace a fresh thrombus.

Coronary thrombosis is almost invariably on the basis of a coronary arteriosclerosis. Often it is only the final event blocking a lumen already greatly narrowed. Paterson³⁹ has emphasized the relation between intimal hemorrhage in a

sclerotic artery and thrombosis of the lumen. The intimal capillaries frequently found in atheromatous lesions are poorly supported by the surrounding soft atheromatous material. Also they are subjected to relatively high intracapillary pressure as they may arise directly from the coronary lumen. Hence they are prone to rupture and the resulting small hematoma may precipitate thrombosis, or by itself



Fig. 104.—Mural thrombus, left ventricle. It is partially organized and attached to a thin area of myocardium, the site of an infarct. (Courtesy Dr. V. Moragues.)

occlude the lumen. Paterson³⁹ has presented evidence that the formation of coronary thrombi may be a gradual process, sometimes occupying several days before occlusion is complete.

Although occlusion by arteriosclerotic thickening of the coronary wall is not infrequent, final complete blockage is

usually by thrombosis in the greatly narrowed lumen. This type of occlusion being gradual, an efficient anastomotic circulation tends to develop. Hence there may be no acute myocardial infarction and no clinical signs and symptoms, although marked scarring results. The great capacity of

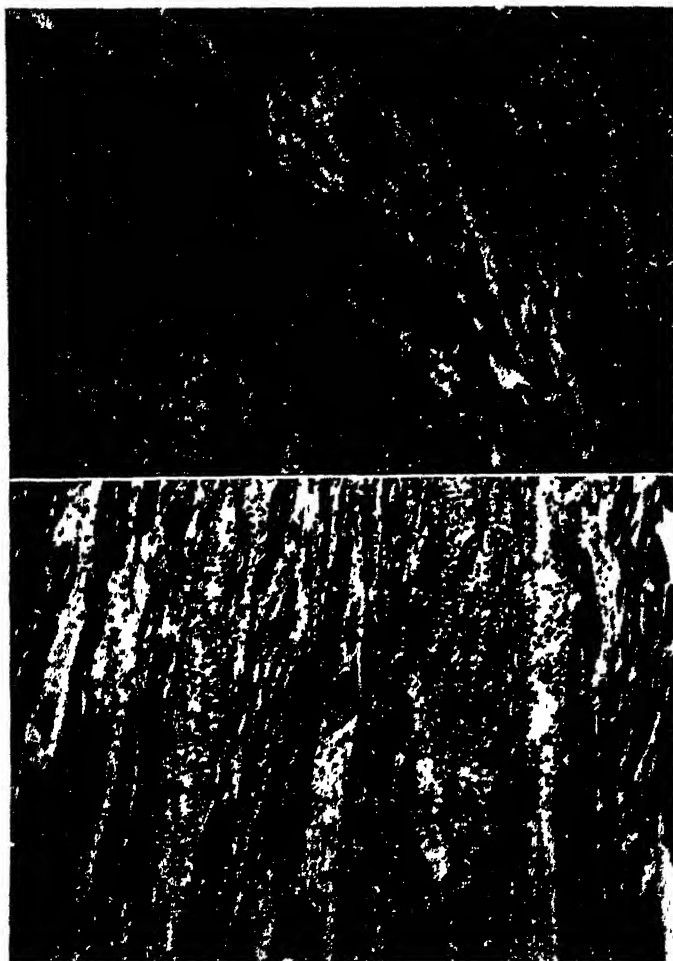


Fig. 105.—Early infarct of myocardium. Note the acute myocarditis, with edema and infiltration of leucocytes. A mural thrombus over the infarcted area occupies the left portion of the upper figure.

anastomotic circulation for compensation in such cases has been emphasized by Blumgart and his colleagues.⁴⁰

Syphilis of the aorta when it involves the region of the coronary ostia may so narrow these openings as to interfere with coronary circulation in much the same fashion as does arteriosclerosis.³⁸

Coronary occlusion by an embolus is relatively rare because of the protected position of the coronary openings. When coronary embolism occurs, it is usually due to a fragment of vegetation from the adjacent aortic valve.

In a small proportion of cases coronary occlusion causes sudden death. This occurs when a sufficiently large area of myocardium is rendered ischemic. The mechanism of death is by ventricular fibrillation or asystole. In such cases a myocardial infarct is not found, because there has been no time for it to develop.

Myocardial Infarction.—Myocardial infarction is usually accompanied by prolonged substernal oppression or pain, shock, electrocardiographic changes, fever, leucocytosis, and increased sedimentation rate. The pathologic changes in an infarct of the myocardium have much in common with infarcts elsewhere, but certain features are peculiar because of the nature and function of the heart. The relative infrequency of infarction involving auricles or right ventricle has been mentioned.

MacCallum and Taylor⁴¹ have pointed out the characteristic position occupied by the myocardial changes following coronary occlusion. Occlusion of the anterior descending branch of the left coronary produces scarring of the anterior part of the interventricular septum, and the apical and anterior part of the wall of the left ventricle. Obstruction of the circumflex branch of the left coronary affects the wall of the left ventricle in its median portion and does not involve the septum. Obstruction of the right coronary produces scarring which involves the posterior half of the interventricular septum, extending backward behind the papillary muscles of the mitral valve, to curve around on the posterior part of the wall of the left ventricle.

While these are the usual and typical areas of myocardial infarction, the location of the coronary occlusion and the site of infarction do not have a constant relationship. Blumgart and his colleagues have demonstrated "infarction at a distance," due to sudden obstruction of one coronary, the

anastomotic circulation from which was instrumental in maintenance of adequate nutrition in an area normally supplied by another coronary.

The appearance of an infarct of the myocardium varies with its age. A visible infarct does not have time to develop if death rapidly follows coronary thrombosis. In early stages an infarcted area may be dark red or hemorrhagic in appearance. Later there appears a mottling of yellowish opaque areas of necrotic muscle in the dark red tissue. Microscopically the necrotic muscle fibers appear swollen, hyaline, and lose their striations and nuclei. Leucocytes abundantly infiltrate the area. The infarcted area undergoes softening (*myomalacia cordis*), which may result in thinning and aneurysmal dilatation of the area, and sometimes rupture. Rupture is most common in the first week and is rare after the second week. Localized pericarditis is present over the area of infarction, and mural thrombi form on the injured endothelium lining the region of infarction.

The healing of myocardial infarcts has been described by Mallory, White, and Salcedo-Salgar.⁴² Necrosis of muscle and leucocytic infiltration are predominant features of the first week. In the second week one sees removal of necrotic muscle and replacement by connective tissue. This is evident grossly as a zone of red, depressed tissue surrounding pale brown areas of necrotic muscle. The new connective tissue lays down increasing amounts of collagen until the area is converted into a firm, grayish, fibrous scar. This process appears to be complete in five to eight weeks, depending on the size of the infarct.

The complications which may follow myocardial infarction include (1) rupture of the heart with rapid death, (2) mural thrombi which may give rise to embolism, and (3) congestive circulatory failure due to insufficient healthy muscle remaining to carry on the work of the heart.

Hypertrophy of the Heart

Increase in size of the heart is the result of increased work thrown upon the organ. The increase in size is due to enlargement of the individual muscle fibers and not to increase in their number. Hyperplasia and regeneration of muscle fibers do not occur in the adult heart. Hypertrophy is often, but not always, accompanied by dilatation.

The average normal male heart weighs 300 grams, and the female heart, 250 grams. Normal heart weight appears to be expressed most easily in terms of height of the individual.²⁸ The left ventricle averages 8 to 10 mm. in thickness, and the right ventricle, 2 to 3 mm. In cases of great hypertrophy, weights may range from 700 to 1000 grams.



Fig. 106.—Hypertrophy of left ventricle, chronic hypertension. Note excessive thickening of wall of left ventricle, as compared with wall of right ventricle. The heart has been cut transversely through the ventricles.

When an unusual amount of work is thrown upon the heart muscle, it attempts to compensate by enlargement of the muscle fibers. The portion of the heart which hypertrophies is determined by the location of the circulatory obstruction against which it must work. Hypertrophy of the left ventricle results from: (1) Hypertension, either primary or associated with chronic glomerulonephritis; (2) aortic regurgitation or stenosis; (3) mitral regurgitation; (4) coronary sclerosis. Hypertrophy of the right ventricle is caused by: (1) mitral stenosis; (2) pulmonary stenosis or regurgitation; (3) increased resistance in the

pulmonary circulation (cor pulmonale) e.g., from emphysema or marked pulmonary arteriosclerosis; (4) coronary sclerosis.⁴³ Also, failure of the left ventricle throws increased work on the right ventricle and may cause hypertrophy.

In infants there occasionally occurs an "idiopathic" hypertrophy, which is due to excessive glycogen content of the myocardium. This condition is related to von Gierke's glycogen storage disease.

Hypertensive Heart Disease

Peripheral hypertension produces hypertrophy of the left ventricle due to its increased load. The hypertension is a disturbance of peripheral arterioles, however, and the cardiac effects are secondary. Coronary arteriosclerosis or other cardiac lesions are not infrequently associated. Eventually the heart may be unable to cope with its increased work, so that dilatation and congestive circulatory failure result. Congestive heart failure causes a considerable proportion of deaths from hypertension.



Fig. 107.—Dilatation of ventricles.

Dilatation of the Heart

Some dilatation of cardiac chambers precedes and accompanies hypertrophy. In addition, an acute dilatation may result from toxic effects on the myocardium, as in diphtheria. Dilatation usually accompanies a failing heart. A localized dilatation may occur in a weakened area of infarction.

Fragmentation of Myocardium

The heart muscle fibers are often seen in microscopic sections to be transversely broken at irregular intervals. The change is apparently an agonal occurrence and is not of significance.

Myocarditis

Myocarditis is an important part of rheumatic fever. Acute myocarditis is frequently associated with bacterial endocarditis. The patchy fibrosis of the myocardium associated with coronary disease is often termed chronic interstitial myocarditis. These types of myocarditis, as well as syphilitic myocarditis, are considered elsewhere. Serum sickness has been reported to have an associated myocarditis.⁴⁵ Interstitial myocarditis with prominent eosinophiles may follow sulfonamide administration (see p. 186).

Toxic myocarditis (parenchymatous myocarditis) is an acute degenerative change in cardiac fibers due to severe acute infections such as diphtheria, typhoid fever, and pneumonia.⁴⁶ The changes in the muscle fibers may be cloudy swelling, fatty, hydropic or hyaline degeneration. Severe degenerative changes may proceed to actual necrosis of some muscle fibers.

Fatty Degeneration of the Heart

In fatty degeneration, fat appears in heart muscle fibers, where normally none is demonstrable. It may affect particularly the endocardial portion of the muscle, so that the abnormal fatty deposits are seen on the inner surface of the heart as a mottling of pale and yellowish flecks and irregular stripes—the so-called thrush-breast appearance. This type of fatty degeneration is particularly characteristic of severe anemias. The heart also may be involved by a more generalized fatty change, in which the whole organ is pale and flabby. Various acute infections and toxic processes tend to produce this latter type of lesion.

Fatty Infiltration of the Heart

Fatty infiltration refers to an abnormal amount of fat in subepicardial tissue, with penetration of the fat between muscle bundles. The right ventricle is most affected. The muscle fibers become atrophic and disappear, with replace-



Fig. 108.—Metastatic melanoma of heart. The black tumor nodules can be seen involving pericardium, myocardium, and endocardium. (Courtesy Dr. V. Moragues.)

ment by fatty tissue. Mild degrees are quite common in association with obesity. In rarer cases in which the fatty infiltration is severe, it may interfere with function and even be a cause of death.

Cardiac Failure

Failure of adequate circulation or cardiac decompensation is a condition in which cardiac output is too low for metabolic needs and in relation to venous return. A number of interrelated bodily changes occur, those most clearly evident anatomically being edema, accumulation of fluid in serous cavities, and chronic passive congestion of various organs such as liver, spleen, kidneys, and lungs. The heart itself becomes dilated.



Fig. 109.—Primary myxomatous tumor projecting into left atrium.

The edema of cardiac decompensation is probably due to the operation of a number of factors, among which elevated venous pressure, changes in capillary and lymphatic function, and excessive sodium chloride intake are frequently of importance⁴⁸ (see p. 62).

Sudden death occasionally occurs,⁵⁰ probably of cardiac origin, but without any demonstrable anatomic changes.

Some of these possibly are due to a reflex inhibition of the heart. Raab⁴⁹ has suggested that excessive accumulation of adrenalin or related substances in the heart muscle may explain some cases of sudden death as well as other functional changes of the myocardium.

Tumors of the Heart

Both primary and secondary tumors of the heart are rare. A congenital striated muscle tumor (rhabdomyoma) is seen chiefly in infants, often in association with tuberous sclerosis. The myocardial fibers forming the tumorlike nodules are distended with glycogen, and it is doubtful that the condition represents a true neoplasm.⁵³ In adults the commonest primary tumor is a polypoid mass arising from one atrium, projecting into the atrial cavity, and predominantly of myxomatous or angiomatous microscopic structure.^{51, 52} While some such atrial polypoid masses are organizing thrombi, others appear to be true neoplasms, and malignant examples have occurred. Malignant melanoma is one of the more frequent types of metastatic tumor.

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CHAPTER XIII

THE KIDNEYS, URINARY TRACT, AND MALE GENITALIA

KIDNEY

Cardiovascular renal disease is a term used broadly to include the vascular and inflammatory disorders of the kidneys, associated vascular lesions of other organs, and the effects on the heart and brain. Collectively, this group of conditions causes about one-third of all deaths and is the cause of death in one-half of individuals over 50 years of age. Little is known about etiology, prevention, or effective treatment.

The kidneys play an essential part in this group of conditions. The renal lesions are of two main types: (1) inflammatory, with primary involvement of glomeruli (glomerulonephritis); and (2) vascular, with primary involvement of arterioles and small arteries, associated with high blood pressure (arteriolar nephrosclerosis, essential hypertension).

Renal Structure and Function

The kidneys are composed of units (nephrons), each consisting of a glomerulus and its associated tubule. A normal human kidney contains about 1.25 million nephrons, sufficient for a considerable reserve. The glomerulus is a collection of capillaries covered by epithelium continuous with that lining the tubule. A thin basement membrane separates the epithelial covering of the glomerular capillaries from the endothelial lining. The total surface of a glomerular tuft is very large, and their aggregate surface is enormous. The glomerulus acts as a filter, and from blood flowing through its capillaries a protein-free filtrate of the plasma collects in the glomerular space and flows down the tubule. During this tubular passage there is active resorption of water, glucose, chloride, sodium, and other substances. Active secretion by tubules of certain substances, notably creatinine and ammonia, may also occur. For this mechanism to function normally in the nephron there must be (1) a free flow of blood through the capillaries of the tuft; (2) a normal filter, i.e., water, salt, urea, and other waste products must

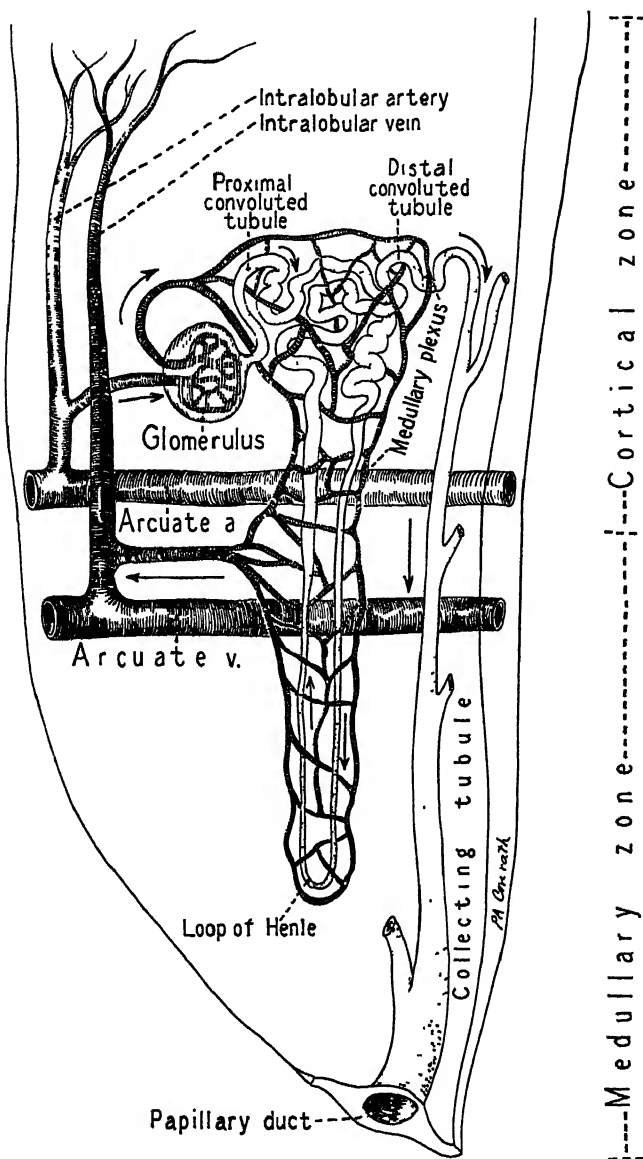


Fig. 110.—Nephron. Diagrammatic representation of a renal unit, showing circulatory relationships.

be allowed to filter through, but certain substances such as plasma proteins held back; (3) a normal epithelial lining of the tubule and an unblocked lumen. Lesions in the kidney can produce functional disturbance by three corresponding types of qualitative change. Each may occur alone, but combinations of varying degrees of each are the usual occurrence. The large numerical reserve of identical units is such that a fraction of their number can maintain adequate function. Consequently, functional changes in relation to renal lesions must be considered on a quantitative as well as a qualitative basis. When functional deficiency occurs in chronic glomerulonephritis and nephrosclerosis, values for urea and creatinine clearance are closely correlated with the number of functioning glomeruli.

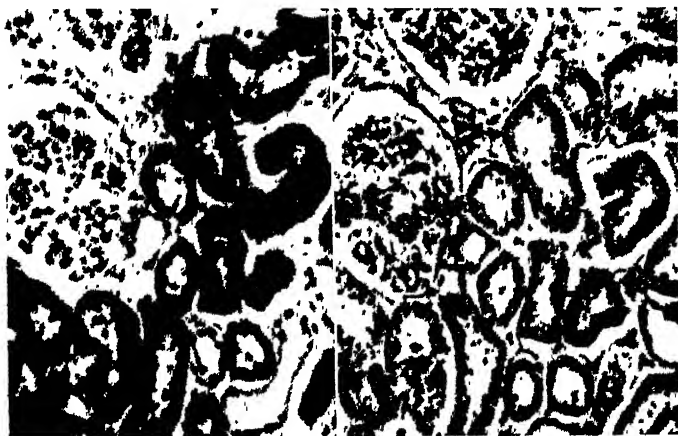


Fig. 111.—Phosphatase in kidney. Black areas (left) indicate site of phosphatase in tubular epithelium, with control stain of same area (right).

The vessels of the glomerular tuft, after forming the efferent arteriole, again break up into capillaries which supply the tubule. Hence, obstruction of flow through the glomerulus also interferes with tubular blood supply. Destruction of a glomerulus usually results in atrophy and disappearance of the corresponding tubule, although aglomerular tubules have been demonstrated by Oliver.¹ Glomeruli do not regenerate. No new glomeruli are formed during adult life, though some compensation may result from hypertrophy of those remaining. Tubular epithelium, on the

other hand, regenerates readily. Hence injurious agents which affect the tubular epithelium alone, e.g., mercury bichloride, lead either to death of the individual or to complete recovery, i.e., the injury is neither chronic nor progressive. Following injury, regenerated tubular epithelial cells may have an atypical flattened form and are more resistant to injury.³

The presence of alkaline phosphatase may be demonstrated in renal tissue by a specific histochemical stain. The enzyme probably has a role in tubular reabsorption of sugar by dephosphorylating hexose phosphates. Decrease of phosphatase is found when there is disturbance of tubular function, as in hydronephrosis.⁵

Glomerulonephritis

In glomerulonephritis the lesion is primarily an inflammation affecting glomerular tufts. This is manifested by (a) proliferation of glomerular and capsular epithelium, (b) proliferation and swelling of capillary endothelium, (c) thickening of basement membranes, (d) formation of intracapillary fibers, and (e) exudation of leucocytes. Either proliferative activity or exudation may be the predominant change. Diffuse involvement of glomeruli is usual, but focal changes may occur as the result of infected emboli. The glomerular changes result in narrowing or complete closure of the capillaries of the tuft. The condition progresses to hyalinization and disappearance of the glomeruli. Secondary degenerative changes in tubules are constantly present.

The exact cause of glomerulonephritis is unknown, but it appears to be related to infection, particularly with streptococci. Acute glomerulonephritis is frequently preceded by an attack of tonsillitis, scarlet fever, or other streptococcal infection. An allergic reaction of renal tissue to bacteria or their products has been suggested as the exciting cause.⁶

Diffuse glomerulonephritis may be subdivided into acute, subacute, and chronic forms. The acute form is more common in children, lasts only a few weeks, and may entirely clear up, or progress to subacute or chronic forms. The subacute type lasts several months, and the chronic form may last many years, often with long periods of latency. The

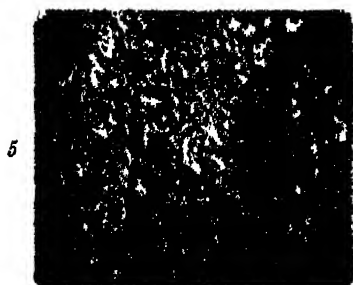
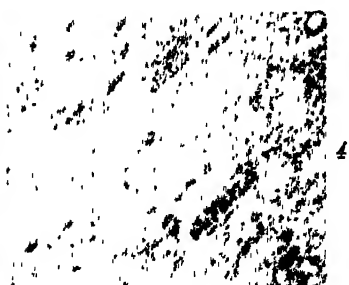
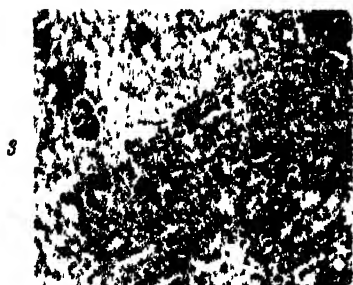


Plate VIII.—Renal lesions: 1 and 2. Acute glomerulonephritis. 3. Acute interstitial nephritis. 4. Transfusion reaction. 5. Amyloidosis. 6. Hyaline droplet degeneration of tubules.

subacute and chronic forms are relentlessly progressive conditions leading eventually to failure of renal function, the final stage presenting a condition referred to as uremia.

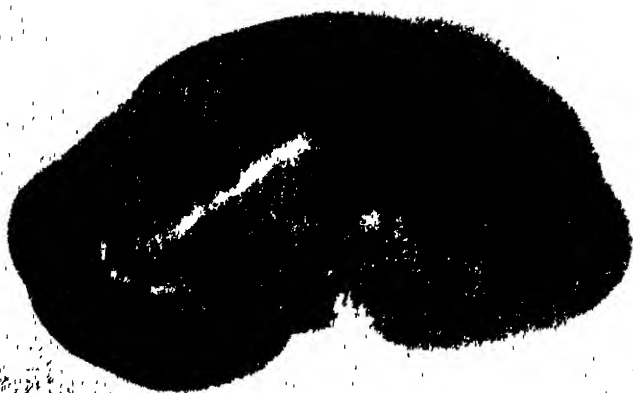


Fig. 112.—Acute glomerulonephritis. (Courtesy Dr. H. C. Schmeisser.)

Acute Diffuse Glomerulonephritis.—In acute glomerulonephritis the kidneys are swollen and pale, with smooth surfaces on which tiny hemorrhages are sometimes visible. Microscopically, the glomeruli appear enlarged, cellular, and

bloodless. Their apparent increase of nuclei is mainly the result of endothelial proliferation, but leucocytes are often numerous. Small hyaline intracapillary fibers are demonstrable by an azo-carmin stain. They increase in size and number, eventually resembling collagen fibers.⁸ Capillary thrombi may be present. The effect of all these changes is to impede or entirely obstruct the flow of blood through the glomeruli. This results in diminished urinary output (oliguria), some hypertension, and leakage of albumin and red cells through the glomerular filter into the urine. Tubular

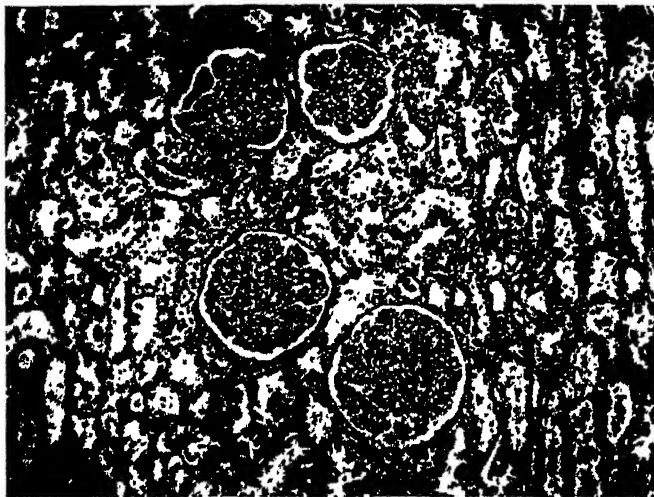


Fig. 113.—Acute glomerulonephritis. Note the large size and marked cellularity of the glomeruli.

changes are usually present as a hyaline droplet degeneration when the inflammatory changes are severe, and as fatty degeneration when the changes are milder. The tubular lesions are due partly to decrease of their blood supply by the glomerular changes, and in part result from a direct toxic action. Severe involvement of a large proportion of glomeruli results in death. Otherwise, there is recovery or progression to subacute or chronic phases.

Subacute Glomerulonephritis.—Glomerulonephritis terminating in uremia in the course of a few months is usually referred to as subacute. The kidneys are enlarged, pale, and soft ("large white kidney"). There may be some slight

irregularity of the surface and some adherence of the capsule. Microscopically, there is fairly uniform involvement of all glomeruli, with frequent and prominent capsular "crescents" due to proliferation of capsular epithelium. Adhesions of tuft to capsule are common. Hyalinized glomeruli

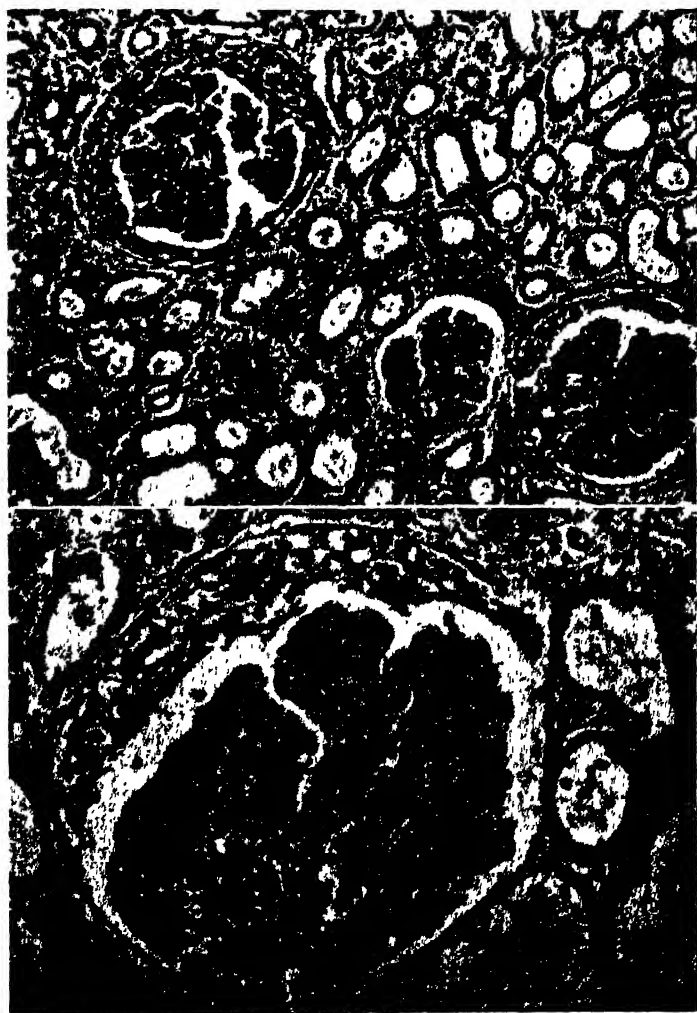


Fig. 114.—Subacute glomerulonephritis. Note the glomerular crescents due to proliferation of capsular epithelium.

are absent or rare. Moderate uniform tubular atrophy is present, and many tubules contain casts. Interstitial connective tissue may appear increased.



Fig. 115.—Chronic glomerulonephritis. Note the granularity of the outer surface, and the irregular narrowing of the cortex. (Courtesy Dr. H. C. Schmeisser.)

Chronic Glomerulonephritis.—Chronic glomerulonephritis ends by failure of renal function. It may result from an acute diffuse glomerulonephritis which progresses to a chronic phase. In such cases the history may be one of infection, an acute attack of nephritis, progression to a chronic

phase and termination, all in a relatively short period. More frequently there is no history of an acute attack, because acute phases were mild and passed unnoticed. The condition may progress over many years, with little clinical evidence except a slowly progressive decrease of renal function. In other cases there are long latent periods of apparent health, punctuated by mild acute flare-ups. The end result in each case is similar, with failure of renal function terminating in uremia.



Fig. 116.—Chronic glomerulonephritis. Note the cellular glomerulus with capsular adhesions, and hyaline casts in tubules.

The failure of renal function is manifested by decreasing ability to concentrate the urine, until there is a fixed specific gravity near 1.010, corresponding to that of blood plasma. The dilute urine is excreted in large amount, resulting in polyuria and nocturia. Albumin and casts are present in the urine, but in small or moderate amounts. High blood pressure develops and increases with the progression of renal failure. Failure to excrete nitrogenous waste products is reflected in an increase of nonprotein nitrogen and urea in the blood. Termination occurs with the clinical syndrome known as uremia.

The kidneys are small, contracted, and firm. Their capsules are tightly adherent, and the outer surfaces are roughly and irregularly granular and pitted. The cortices are irregularly narrowed and scarred, with loss of normal architectural

markings. Microscopically, a large proportion of glomeruli are partially or completely changed into hyaline masses. Many tubules are atrophic or have disappeared, and the amount of connective tissue between the tubules and glomeruli shows



Fig. 117.—Chronic nephritis. Upper: Chronic glomerulonephritis. Note the capsular adhesions of the glomerular tuft, and the thickening of blood vessels. Lower: Chronic nephritis, from a case of renal dwarfism. Note that tubules are scarce, and the scarred glomeruli form rounded hyaline masses.

a great relative increase. Some tubules and glomeruli are permeable and apparently functioning, though none may be completely normal. Medium-sized and small arteries commonly develop intimal and medial proliferation and thickening. Renal ischemia due to the glomerular and vascular changes results in the hypertension of chronic nephritis. In some cases the gross and microscopic changes of chronic glomerulonephritis are not readily distinguishable from those of the primarily vascular condition, hypertensive nephrosclerosis.

More severe vascular changes, particularly cellular intimal proliferation and arteriolar necrosis, are associated with accelerated progress of the disease in late stages. Such cases clinically may simulate "malignant hypertension," with very high blood pressures and retinal lesions.⁹

Uremia.—Uremia is the complex clinical condition marking the final stage of renal insufficiency. No particular substance or "toxin" is known to be causative, but it is probably an autointoxication due to retention of various metabolic products ordinarily eliminated by the urinary mechanism.¹⁰

Failure of function is denoted by inability of the kidneys to produce a concentrated urine and to adapt to increased work. In final stages of failure the specific gravity of the urine tends to be fixed about 1.010, the urine being practically isotonic with serum. Urea, creatinine, uric acid, sulfate, chloride, ammonia, and phosphate are retained. The hydrogen-ion concentration of the urine can no longer be varied to suit the body's need, and there is frequently a retention acidosis which may be lessened by increased breathing and loss of acid through vomiting. Blood phosphorus increases greatly and calcium falls, resulting in nervous hyperirritability and muscular twitchings. Convulsions may occur when the uremia is associated with hypertension.

Other than the damaged kidneys, there are no constant anatomic changes in uremia. Edema of the brain is common. A mild sterile pericarditis is occasionally present, and degenerative changes have been described in outer portions of myocardium. Necrotizing colitis is an occasional occurrence in uremia (see p. 478).

In occasional cases of widespread renal damage there is excessive loss of water, sodium and chloride. This is an electrolyte disturbance resembling that of Addison's disease (adrenal cortical deficiency—see p. 547), which may be simu-

lated clinically. However, such "salt-losing nephritis" is not benefited by adrenocortical hormone.¹¹

Renal Edema.—Edema in nephritis is influenced by two factors: (1) loss of plasma albumin and (2) salt retention. The albuminuria is due to increased permeability of the glomerular tufts, and the protein loss decreases the osmotic pressure exerted by plasma colloids to hold fluid within the vessels. The sodium chloride retention is due to lessened ability of the damaged kidney to excrete it. Lowering of plasma albumin is the more important factor. Edema tends



Fig. 118.—Embolie glomerulonephritis. Petechial hemorrhagic areas are to be seen on the surface of kidney.

to appear when plasma protein is lowered to 2.5 per cent (normal is about 4 per cent). Loss of albumin is particularly important, because it exerts four times the osmotic force of globulin. In the so-called "nephrotic" types of renal disease a massive albuminuria and severe edema go hand in hand (see p. 300).

The distribution of edema in nephritis is often independent of gravity and may appear first on the face rather than in dependent parts. The edema fluid has a very low protein content and low specific gravity.

Vascular Disease of the Kidney

Sclerosis of renal arteries and intrarenal vessels is extremely important because of the association of these changes with high blood pressure. Ischemic renal tissue releases into the blood stream a pressor substance which produces hypertension by constriction of peripheral vessels. Hypertension may be the result of atherosclerosis of a renal artery in those rare instances in which the lumen is constricted sufficiently to cause renal ischemia.⁷ In the usual case of hypertension, however, renal ischemia is associated with sclerosis of the smallest arteries or arterioles of the kidney. Sclerosis of the larger arteries within the renal substance is usually irregular and not generalized in its distribution. Hence it rarely results in ischemia of sufficient renal tissue to produce hypertension, nor is there enough destruction to cause renal failure. It produces a few large, gross scars, similar to healed areas of infarction. Because it is a common finding in the elderly, such a kidney is called a "senile arteriosclerotic kidney."

The Senile Arteriosclerotic Kidney (Atherosclerotic Nephrosclerosis).—The atherosclerotic involvement of larger and medium-sized intrarenal arteries is a patchy change which results in irregular depressed areas on the kidney surface. The kidney is not much decreased in size unless there is some other pathologic change. Microscopically, fibrous replacement of glomeruli and tubules is present in the scarred subcapsular portions of the cortex. There is some cellular infiltration by lymphocytes and plasma cells. These changes in the kidney rarely are associated with any marked hypertension or renal functional failure.

In some cases an atherosclerotic lesion of a renal artery, usually at or near its aortic opening, sufficiently narrows the lumen to produce renal ischemia and hypertension.

Hypertension.—Cases of high blood pressure commonly are divided into "secondary" and "essential" types. The less common secondary type is the result of glomerulonephritis, or of an adrenal or pituitary tumor. The common "essential" hypertension was so called because there seemed to be no primary lesion. It has been recognized that renal arteriolar sclerosis is an almost constant post-mortem finding in essential hypertension. Moritz and Oldt¹³ have indicated the reasons for considering this a primary change, rather than the result of hypertension. The arteriolar sclerosis is often a generalized change, particularly common in

spleen, pancreas, adrenals, and brain, but it is only in the kidneys that arteriolar sclerosis and hypertension seem to be closely associated. However, biopsy of the kidneys in hypertensive patients has shown that as many as 28 per cent may have little or no vascular change.¹⁴

The importance of renal vascular changes in hypertension has been shown by Goldblatt, who produced renal ischemia by means of a clamp on the renal artery. It was demonstrated that the ischemic renal tissue released a pressor substance into the circulation, which by constrictive action on peripheral vessels produced hypertension.

A pressor substance ("renin") has been extracted from renal tissue. It is a thermolabile, enzyme-like substance which requires for its activity a protein-like substrate present in normal serum ("renin-activator"). The product of their interaction ("angiotonin") produces a prolonged rise in blood pressure.^{15, 16} As a possible origin of pressor substance, the "juxta-glomerular" or "preglomerular cellular apparatus" has been suggested. This is a collection of granular cells in the afferent arterioles of the glomeruli. While these cells have been noted to increase in number and prominence in experimental hypertension in animals,¹⁷ there appears to be no parallelism between the degree of development of these cells and hypertension in man.¹⁸

Essential hypertension has been divided into "benign" and "malignant" clinical types. They appear to be fundamentally the same in nature. The "malignant" form more commonly occurs in young adults. It is more rapidly progressive and has severer lesions, but it is of the same general type, and death usually results from renal failure. Pathologically, the malignant form is characterized by necrosis in the walls of small arteries and arterioles, and small hemorrhages from the severely damaged vessels. These necrotizing vascular changes can be reproduced experimentally by renal ischemia sufficient to cause renal failure.

Common causes of death in hypertension are cerebral hemorrhage, renal failure (uremia), congestive heart failure, and coronary occlusion. Cardiac hypertrophy (left ventricle) is a constant finding in cases of hypertension. Retinal changes¹⁹ are also a constant part of hypertensive disease and consist of sclerosis of small retinal vessels, small hemorrhages, and edema. In the malignant phase retinal changes are severe and may result in blindness.

The basic causation of hypertension is still unknown. Hereditary and racial tendencies are important. The American

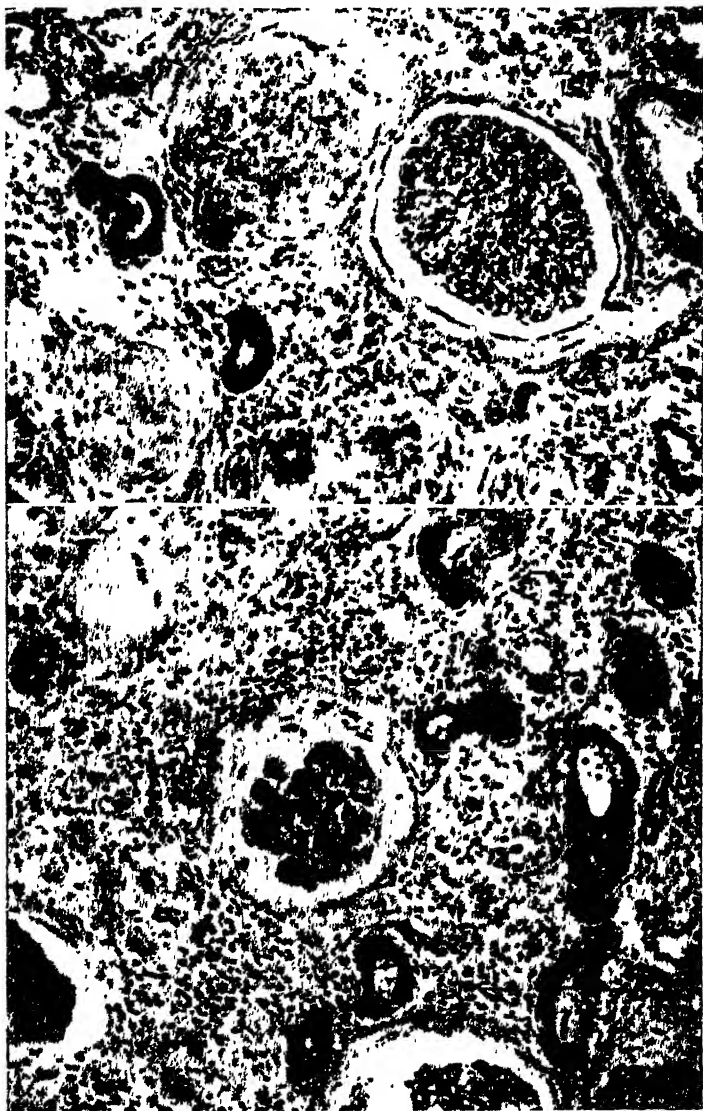


Fig. 119.—Arteriolar nephrosclerosis. From a case of severe hypertension. Note the extreme hyaline thickening of the arteriolar walls, and also the glomerular changes.

Negro has hypertension more frequently and in severer form than white people in the same climate.¹⁹ Body build and, to a lesser degree, obesity seem to have some association with hypertension.²⁰

THE KIDNEY OF HYPERTENSION (Arteriolar Nephrosclerosis).—In hypertension the most constant finding in the kidney is a sclerosis of arterioles. Often the smallest preglomerular vessels show the change most severely in the portion just proximal to the tuft. In many cases the kidneys are of normal size and have smooth surfaces. With more severe or prolonged hypertension any degree of atrophy may be found.



Fig. 120.—Kidney of malignant hypertension, showing focal hemorrhages from arteriolonecrosis.

The capsules are adherent, and the outer surfaces of the kidneys present a finely granular and scarred appearance. Tiny retention cysts are often present in the cortex. For such changes of vascular origin, the term “primarily contracted kidney” is used to distinguish it from the “secondarily contracted kidney” of glomerulonephritis. In practice it is often

impossible to distinguish grossly the contracted kidney of hypertensive nephrosclerosis from that of chronic glomerulonephritis.

In malignant hypertension the kidneys often show but little atrophy, due to rapid progress of the disease. Small hemorrhages on the outer surface of the kidney may cause it to resemble the "flea-bitten" kidney of embolic glomerulonephritis.

Microscopically, the essential lesion is a sclerosis of small arteries and arterioles (see p. 231). The effects of the vascular changes are reflected in the glomeruli, which early show a thickening of the capillary basement membranes, and later varying degrees of hyalinization and atrophy. Glomerular capsules as well as tufts become thickened and hyalinized. The atrophy of glomeruli and associated tubules produces the renal shrinkage.

In malignant hypertension the important change is an acute necrotizing arteriolitis and arteritis. The pathologic findings differ somewhat, depending on whether the hypertension was malignant from the beginning, or a benign hypertension with a superimposed malignant terminal phase. In the latter case, varying chronic changes with hyalinization and atrophy of glomeruli are present, but in addition to the usual arteriolar sclerosis, one sees a hyaline necrosis of vessel walls, some inflammatory cellular infiltration and often hemorrhage about severely injured vessels. The hyaline necrotic changes may extend to involve glomerular capillaries as well as arterioles and small arteries.

In end stages with marked renal contraction, it is often difficult to distinguish chronic glomerulonephritis and arteriolar nephrosclerosis, even by microscopic examination. Remaining traces of a proliferative inflammatory process, e.g., glomerular crescents, must be searched for as a distinguishing feature.

While most cases of hypertension are associated with vascular and renal diseases, a few are due to involvement of endocrine glands or nervous system. Cushing's syndrome (pituitary basophilism), tumors of adrenal glands, and diseases of the brain stem may be associated with high blood pressure.

Orthostatic Albuminuria.—Orthostatic albuminuria is a clinical condition in which there is urinary excretion of albumin when the individual is erect, but not when lying down. Apparently it is due to circulatory changes with variation of position. Abnormalities described in such cases include (1) compression of the left renal vein between the

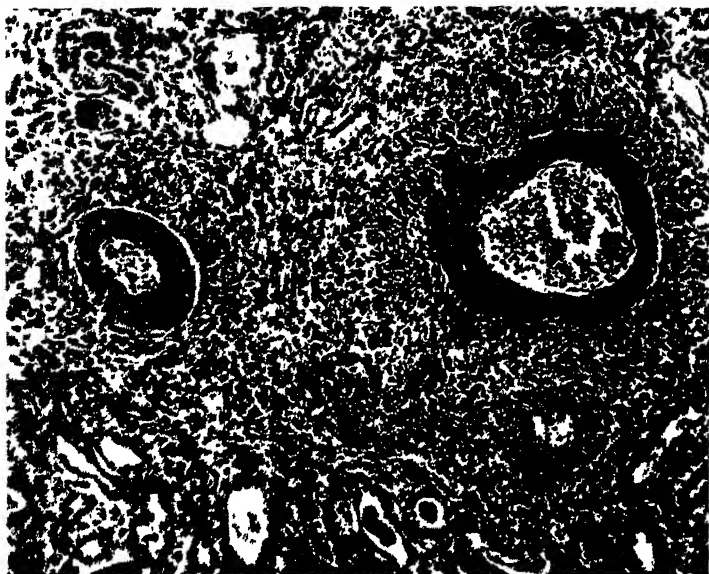


Fig. 121.—Kidney, periarteritis nodosa.



Fig. 122.—Cortical necrosis of kidney. A reddened congestive zone outlines the opaque necrotic cortical tissue.

superior mesenteric artery and the aorta, (2) mobile kidneys, and (3) reduplicate ureters and pelves.

Bilateral Cortical Necrosis of the Kidneys.—There is an unusual condition of extensive necrosis of the peripheral layers of renal cortices which is of unknown etiology, but sometimes associated with toxemias of late pregnancy, or acute infections. A similar condition results from poisoning by dioxane or diethylene glycol, or from choline deficiency in experimental animals. The chief clinical feature is oliguria, and death usually results in a few days. The mechanism is a disturbance in the terminal arteries and arterioles of the renal cortex. Because of ischemia irregular areas of necrosis involve the cortical portions of both kidneys. The surface is mottled by patchy opaque areas of reddish-yellow color and soft consistency. The microscopic appearance is similar to that of infarction, with a zone of congestion and leucocytic infiltration about the margin of the necrotic areas.^{23, 24}

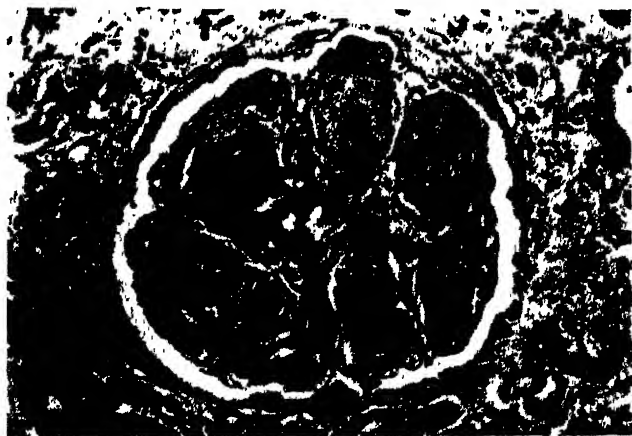


Fig. 123.—Diabetic intercapillary glomerulosclerosis. (U. S. Army Medical Museum, courtesy Major Arthur C. Allen.)

Intercapillary Glomerulosclerosis.—This characteristic glomerular lesion occurs in one-third of diabetics over the age of 40, has no relationship to the degree or duration of the diabetes, but is a helpful criterion in histologic diagnosis of diabetes mellitus. Glomeruli show focal areas of hyaline sclerosis, intercapillary in position or within capillary

walls.^{25, 26} In some cases a clinical syndrome is present which consists of diabetes, hypertension, retinal arteriosclerosis, albuminuria, and edema.

Interstitial Nephritis

Interstitial nephritis, unlike glomerulonephritis, is essentially an exudative rather than a proliferative inflammation. Marked exudates of inflammatory cells may be present focally or diffusely in interstitial tissues.

Acute Diffuse Interstitial Nephritis.—Acute interstitial nephritis occasionally develops in association with certain acute infectious diseases, e.g., diphtheria, scarlet fever, Weil's disease, etc. Grossly the kidney is large, pale or mottled red and gray, and soft. The cortex is thickened.



Fig. 124.—Suppurative pyelonephritis. (Courtesy Dr. H. C. Schmeisser.)

The capsule strips easily. Microscopically there is a focal or diffuse interstitial infiltration of leucocytes, mainly plasma cells, lymphocytes and eosinophiles, but often polymorphonuclear leucocytes as well. It must be distinguished from a leucemic infiltration. The tubules show degeneration but glomerular lesions are usually absent, and the damage is not permanent.

Chronic Interstitial Nephritis.—The rare condition of chronic interstitial nephritis develops as a result of certain types of chronic renal injuries, e.g., in chronic hyperparathyroidism, multiple myeloma, etc. It is characterized by interstitial infiltration by lymphocytes and plasma cells, with degeneration, atrophy, and fibrosis of renal tissue. Distinction from chronic pyelonephritis may be difficult.

Syphilitic Nephritis.—Rich²⁷ has described renal changes associated with syphilis, characterized grossly by tiny glistening grayish-yellow flecks and streaks of the cortex, and microscopically by focal interstitial accumulation of mononuclear cells, mainly lymphocytes. These nodular masses encroach



Fig. 125.—Kidney with dilated double ureters and pelvis. There is hydronephrosis, and irregular scarring of the kidney due to chronic pyelonephritis. (Courtesy Dr. H. C. Schmeisser.)

upon cortical tubules, project into them, and often narrow the lumens. Crystals, or cleft-like spaces left by dissolution of crystals, are found in adjacent tubules. Spirochetes were not demonstrated in these lesions.

Focal Suppurative Interstitial Nephritis (Pyemic Kidney, Abscesses of Kidney).—Lodgment of infected emboli, as part of a generalized pyemia, results in multiple abscesses throughout the kidney substance. The abscesses appear as small, rounded, yellowish opaque areas, surrounded by a red-dened hyperemic zone. They may be numerous or a single

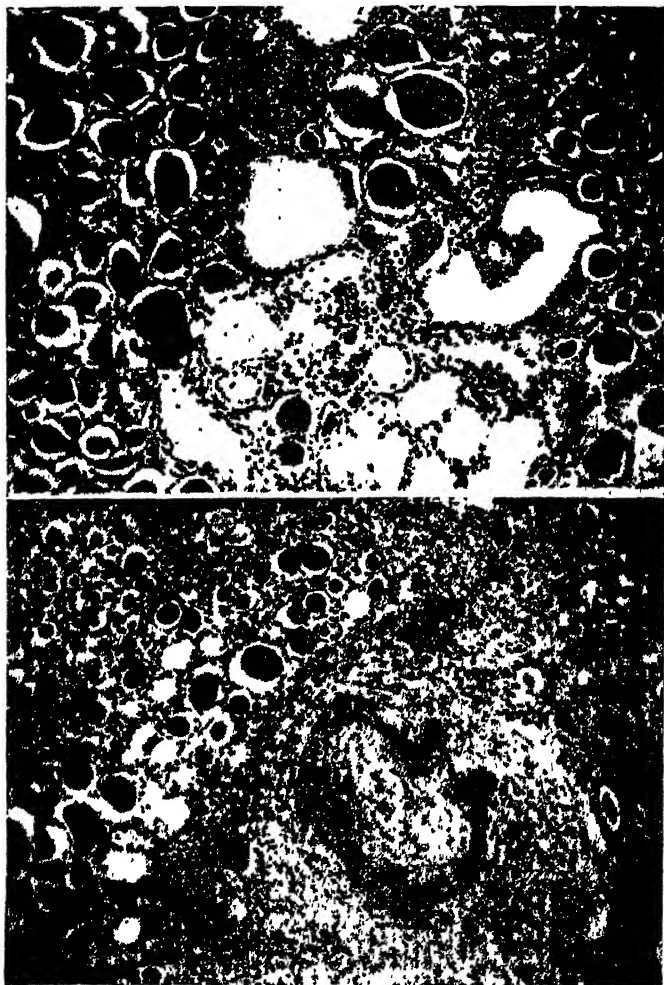


Fig. 126.—Chronic pyelonephritis. Note the dilated tubules filled with casts and the thickened blood vessels.

large abscess ("carbuncle") may be found. Staphylococci and *B. coli* are the common organisms.

Pyelonephritis.—The term pyelonephritis is used when both the parenchyma of the kidney and the renal pelvis are involved by interstitial inflammation. Descending and ascending types are described. In the former, bacteria reach the kidney by the blood stream, primarily infecting renal tissue and "descending" to infect the pelvis. In the latter case the bladder and pelvis are infected first and spread occurs by "ascending" to infect renal tissue. Descending infection is more common. Ascending infection probably occurs only when there are obstruction and consequent stagnation of urine. The so-called "pyelitis" common in children and pregnant women is really pyelonephritis.

The kidneys show wedge-shaped areas of inflammation extending through cortex and medulla to pelvis. Microscopically, such areas show interstitial infiltrations of inflammatory cells, often with some tubular destruction and abscess formation. In the acute stages, the cells are mainly polymorphonuclear leucocytes, and in chronic phases are lymphocytes and plasma cells. The mucosa of the pelvis is roughened, and masses of lymphocytes are found under the epithelium. Continuation of low-grade interstitial inflammation results in gradual atrophy and destruction of tubules, and hyalinization of glomeruli by a process of periglomerular fibrosis and capsular thickening. Colloid casts are present in enlarged tubules with atrophic epithelium. Eventually there results a kidney which is coarsely pitted by U-shaped scars, greatly contracted, and of little functional value. Such a pyelonephritic contracture of the kidney is usually unilateral and must be distinguished from unilateral renal hypoplasia. When chronic pyelonephritis is bilateral, its end stages are easily confused clinically with chronic glomerulonephritis. Vascular changes and hypertension are frequently associated with chronic and healed stages of pyelonephritis.²⁸

Pyonephrosis.—When an obstructive factor is added to pyelonephritis, hydronephrosis and hydronephrotic atrophy are also present in variable degree. When the distended hydronephrotic pelvis is filled with pus, the condition is referred to as pyonephrosis. The end result may be a thin-walled sac filled with pus.

Nephrosis (Tubular Nephritis)

Nephrosis refers to degenerative renal changes, as distinct from inflammation (nephritis) or vascular disease (nephro-

sclerosis). The degenerative changes are seen in the tubules, and particularly in the sensitive convoluted tubules of the cortex. A certain amount of tubular degeneration accompanies glomerulonephritis. Other types are (1) lipid nephrosis, (2) nephrosis of toxic or metabolic origin, and (3) nephrosis resulting from chemical poisons.

Lipoid nephrosis is a type having a peculiar fatty accumulation in tubular epithelium, and clinically characterized by massive albuminuria and marked edema. Cases so termed are usually but a stage in glomerulonephritis although true lipid nephrosis also probably occurs as a rare distinctive disease. The term "lipoid nephrosis" or simply "nephrosis" is often used clinically in a broad way to include all cases of renal disease with marked albuminuria and edema, decrease of plasma proteins with reversal of the albumin-globulin ratio, hypercholesterolemia, normal blood pressure, and normal blood nitrogen. Red blood cells are not found in the urine in abnormal number. A deficiency in plasma amino acids marks crises of the disease in children. It should be noted that albuminuria is a manifestation of hyperpermeability of glomeruli, and not the reflection of a tubular lesion. Pure tubular injuries result in oliguria or anuria. Tubular epithelium regenerates readily, so that if an individual survives a severe tubular injury, recovery is usually complete.

Thus in lipid nephrosis the main functional change lies in the glomeruli, though morphologic changes in them may not be evident. In the rare cases of true lipid nephrosis, which occur only in children and young adults, the prognosis is relatively good, and when death results, it is usually due to peritonitis (often pneumococcal) or infection elsewhere rather than to renal failure. The possibility must be considered that lipid nephrosis is primarily a metabolic disturbance of proteins or lipids, and that the renal changes are but secondary manifestations.

The kidney is enlarged, smooth, and pale, with a thickened light yellow cortex. Microscopically, the swollen convoluted tubular epithelium is filled by fatty droplets. Some of this is neutral fat, but much consists of an ester of cholesterol, which appears doubly refractive through crossed Nicol's prisms. In the pure type glomerular changes are not obvious. There have been described an increased number of lipid-filled endothelial cells lining glomerular capillaries, and a thickening and abnormal porosity of the glomerular basement membranes.⁸⁰

Nephrosis of toxic or metabolic origin is the commonest form of tubular change. Most acute infections and toxic conditions cause tubular lesions, which may be cloudy swelling, fatty degeneration, hyaline droplet degeneration, or necrosis of epithelial cells, in increasing order of severity. Hyaline and lipid droplets indicate absorption from the tubular lumens and storage in the lining epithelial cells of protein and lipid material which has passed through damaged abnormally permeable glomeruli.³² Cholemic nephrosis is a tubular degeneration accompanying severe jaundice. It is uncertain whether it is due to bile pigments, bile salts, or associated liver damage. Intestinal obstruction, particularly when high in the intestinal tract (e.g., pyloric stenosis), may produce tubular degeneration, sometimes with calcification of the degenerated cells.^{33, 34}



Fig. 127.—Hydropic degeneration of the kidney. (Due to intravenous injection of hypertonic sucrose.) (From South. M. J. 34: 257, 1941.)

Excretion of Bence-Jones protein in the urine (in multiple myeloma and other skeletal lesions) produces some tubular degeneration. Precipitation of the protein with blockage of the tubular lumens also occurs.

Chemical nephrosis is due to a variety of poisons which cause degeneration and necrosis of tubular epithelium. Mercury bichloride, a frequent example, causes a pure tubular

injury of severe grade and results in oliguria, which usually progresses to anuria and death in uremia. Death occurs most frequently between the fifth and tenth days, at which stage the kidney is swollen and grayish white in color. The epithelium, particularly of the convoluted tubules, is necrotic, broken up, and irregularly desquamated. The interstitial tissue is edematous and often infiltrated by leucocytes. After seven or ten days the kidney appears more red and congested, and calcium is often deposited in the degenerated and necrotic tubular epithelium. Evidence of epithelial regeneration and mitotic nuclei may be found at this time. (See Fig. 66, p. 183.) In experimental animals testosterone gives some protection against the damaging effects of mercury bichloride³⁵

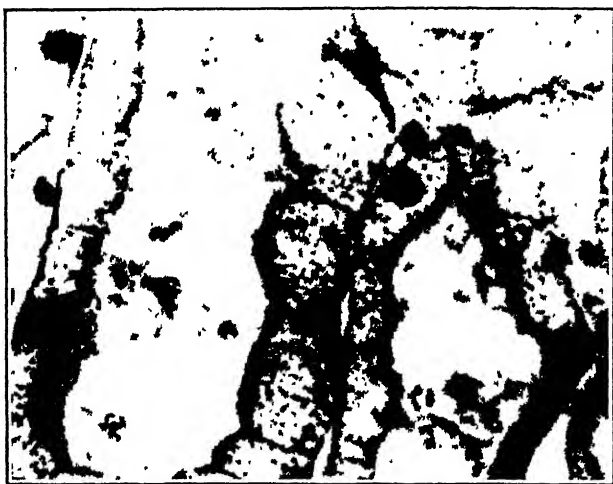


Fig. 128.—Hydropic degeneration. High magnification of renal convoluted tubules, showing hydropic degeneration due to hypertonic sucrose. (From South. M. J. 34: 257, 1941.)

Hyperparathyroid Renal Disease

Renal Hyperparathyroidism.—Deficiency of renal function stimulates hyperplasia and hyperfunction of the parathyroid glands. The actual stimulating factor is probably some disturbance of calcium or phosphorus balance resulting from renal deficiency. Parathyroid hyperplasia and hyperfunction are present in some degree in all cases having marked deficiency of renal function. If the disturbance is severe and

long continued, a clinical picture is produced similar to osteitis fibrosa cystica or renal rickets (in children).

Parathyroid Nephritis.—Hyperparathyroidism itself may produce renal lesions of a distinctive type and result in renal failure. The parathyroid hyperfunction may be due to a localized adenomatous overgrowth of a single parathyroid or to a peculiar diffuse hypertrophy of all the parathyroids. The resulting disturbance in calcium metabolism appears to be the main cause of the damage to the kidney. Calcium deposits in the kidney are the characteristic feature. In acute hyperparathyroidism the calcium may be mainly intratubular, but in chronic hyperparathyroidism it is interstitial and peritubular and is accompanied by interstitial fibrosis and cellular infiltration. Renal calculus formation is very frequent and develops on the basis of a parenchymal calcium concretion. Hyperparathyroidism is, however, the underlying cause of only a very small proportion of renal calculi.²⁶



Fig. 129.—Chronic pyelonephritis. The external surface of the atrophic kidney is scarred and irregular.

Renal Rickets.—Renal rickets (renal dwarfism, renal infantilism), is a condition arising before puberty, in which a prolonged chronic renal insufficiency is associated with stunting of growth, skeletal deformities, and sometimes failure of sexual development. Common clinical features are polyuria, polydipsia, high blood phosphorus, nitrogen retention, and low blood pressure despite renal failure. Renal disease develops before bone growth is completed and gives rise to renal

insufficiency continuing over a long period. The failure of renal function causes retention of phosphates. A high level of blood phosphorus is characteristic and, in turn, stimulates the parathyroids to hyperplasia and increased function. The bone lesions, particularly in those cases with marked deformities, are those of osteitis fibrosa cystica and due to excess of parathyroid hormone. Excess phosphates excreted by way of the intestine may combine with ingested calcium to form unabsorbable salts. In this manner true calcium starvation is added to the picture. In such cases the blood calcium is low, there is failure of bone growth (dwarfism), and bone lesions more nearly resemble true rickets.



Fig. 130.—Chronic pyelonephritis and hyperparathyroid renal disease. Black calculous masses are evident in the renal substance and in the pelvis. From an individual having hyperparathyroidism due to a parathyroid adenoma.

The actual lesions in the urinary tract can be divided into two groups. In one there are lesions of a congenital nature, either cystic kidneys or some abnormality of the lower urinary tract resulting in dilatation of ureters and hydronephrosis. In the other group the renal changes have commonly been called chronic interstitial nephritis. Here there is advanced glomerular hyalinization or destruction but with little evidence of antecedent glomerulonephritis, such as crescents in Bowman's capsule. The tubules may be dilated or may have largely disappeared, their place being taken by chronic inflammatory cells and fibrosis in interstitial tissues. Small amounts

of calcium are often present in interstitial tissue. In such cases the picture is that of the end stage of chronic pyelonephritis or of a kidney damaged by chronic hyperparathyroidism. In some of these cases the changes are due to a metabolic disturbance or cystin diathesis and cystinuria, which results in marked interstitial nephritis and renal atrophy.^{37, 38}



Fig. 131.—Calcium deposit in the cortex of the kidney. Part of the calcium is interstitial and part intratubular. (From *J. Urology* 44: 29, 1940.)

Renal Calculi

Stones or calculi formed in the urinary tract are due to precipitation of chemical salts in the urine. Calculi are frequently classified as primary and secondary. The primary stones are those formed without apparent causal factors, such as infection, inflammation, or urinary obstruction and stasis. Secondary stones are those which follow evident inflammation or obstruction.

Etiology.—The several factors which may play a part in stone formation, singly or in combination, are:

1. High concentration of crystalline salts in the urine favors precipitation. Colloids in the urine hold the crystalloids in solution in a super-saturated state. The balance is delicate and easily disturbed either by hyperexcretion of

crystalloids, such as may occur in hyperparathyroidism, or by decrease of colloids, which may be due to infection. The result is precipitation of the crystalline matter and colloids, the colloidal gel forming an organic framework.

2. **Encrustation of solid material with urinary salts** is a factor of importance. A nidus for such precipitation may be

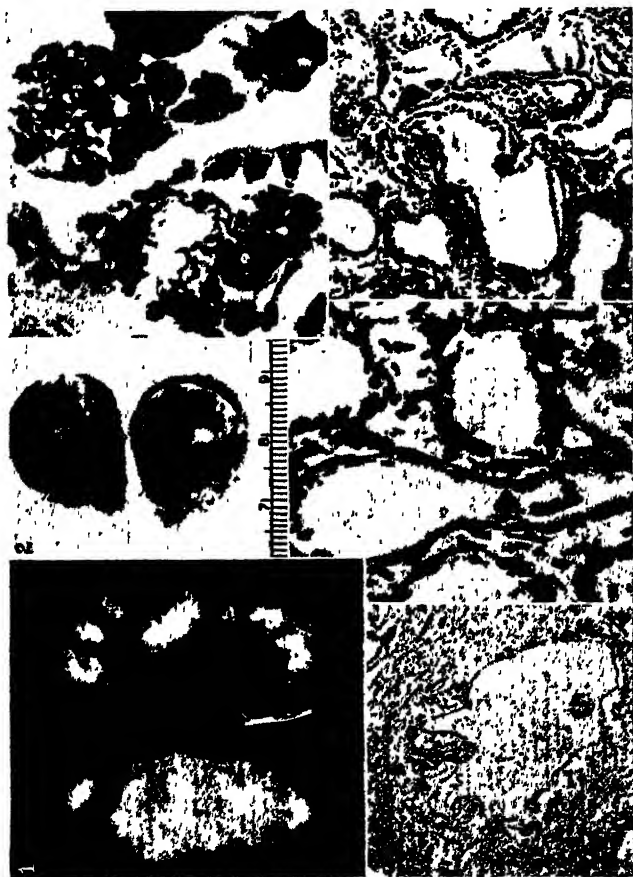


Fig. 132.—Hyperparathyroid renal disease. 1. X-ray of kidneys in a case of hyperparathyroidism, showing massive deposits of calcium. 2. Parathyroid adenoma in this case, as seen from the external and cut surface. The dark area on the cut surface is a region of hemorrhage (scale in centimeters). 3, 4, 5, and 6. Interstitial and paratubular calcium deposits in the kidney. (From *Endocrinology* 24: 372, 1939.)

bacteria, necrotic or degenerated tissue, or other foreign bodies. The association of many calculi with bacterial infection has been proved. Randall has described the mechanism by which encrustation frequently occurs on a small calcified plaque of a renal papilla.³⁹



Fig. 133.—Calcification in a renal papilla. The dark masses represent interstitial and intratubular calcium deposits. (From *J. Urology* 44: 29, 1940.)

3. **Vitamin A deficiency**, known to produce changes in the epithelial lining of the upper urinary tract, has been effective in the experimental production of stone. How important a factor this may be in man is still uncertain.

4. **Urinary reaction** is important in maintenance of urinary salts in solution and largely determines the composition of the stones. However, reaction alone, e.g., marked alkalinity, is probably never the cause of stone formation.

5. **Urinary obstruction** acts by promoting stagnation and infection. It is rarely the sole factor.



Fig. 134.—Renal calculus. Calcium plaque in tissue of a renal papilla with attached early stone. Note the narrow neck-like attachment of the calculus, and its laminated structure due to successive deposits of precipitated material. (From *J. Urology* 44: 29, 1940.)

6. **Hyperparathyroidism** has a known direct relationship to renal stone formation but probably accounts for 1 per cent or less of renal calculi. The greatly increased urinary



Fig. 135.—Calculous pyonephrosis. Stones are evident in the greatly dilated pelvis of the kidney. The normal markings and architecture of the kidney are destroyed. (Courtesy Dr. H. C. Schmeisser.)

excretion of calcium and phosphorus in the urine and the tendency to deposition of calcium salts in renal tissue result in calculus formation in 30 to 70 per cent of cases of hyperparathyroidism.

Pathogenesis.—The mechanism of primary stone formation has been described by Randall.³⁰ Damage to a renal papilla results in calcium deposit in the injured tissue. When near the surface, this plaque of calcium becomes exposed by ulceration of overlying tissue and becomes a nidus on which any urinary salt may crystallize. Successive depositions produce a laminated stone, often of variable composition. The plaque holds the stone in place until it has time to reach a considerable size before tearing away from its moorings.

Types.—While most stones are composed of mixtures of uric acid, calcium oxalate, and ammonium-magnesium phosphate, certain constituents predominate and give the stone distinctive character. **Uric acid stones** are brown, fairly smooth, moderately hard, and on section show concentric laminations. **Oxalate stones** are very hard, have a rough spiny surface of dark brown color, and are laminated. **Phosphate stones** are soft, smooth, white, and friable. Uric acid and oxalates tend to precipitate in an acid urine, while phosphate stones are commonly associated with alkaline urines.

Sulfapyridine administration may be associated with the formation of small stones, due to precipitation of acetylated sulfapyridine.

Effects.—Renal calculi may obstruct the outflow of urine, promote infection, and cause the pain of renal colic. The point of obstruction may be in the renal pelvis, ureters, or bladder. Partial or intermittent obstruction gives rise to dilatation of ureter or renal pelvis (hydronephrosis) above the obstructed point. Stasis due to obstruction promotes infection (pyelonephritis). Passage of a small stone through the ureter produces the severe pain of renal colic.

Hydronephrosis

Hydronephrosis is a dilatation of the renal pelvices and associated atrophy of renal tissue resulting from an obstruction to the outflow of urine. Obstruction may be due to a wide variety of causes, the most common of which are inflammatory stricture, pregnancy, and pressure by tumors. Obstructions at or below the opening of the bladder result in bilateral hydronephrosis. With obstruction of one ureter,

only the corresponding kidney is hydronephrotic. The degree of hydronephrosis depends upon the degree and duration of the obstruction. Partial and intermittent obstructions result in a greater degree of hydronephrosis than do sudden



Fig. 136.—Hydronephrosis. Due to obstruction of the upper end of the ureter. (Courtesy Dr. H. C. Schmeisser.)

complete obstructions. The latter tend to produce atrophy with relatively little hydronephrosis. In some cases no mechanical obstruction can be demonstrated (idiopathic hydronephrosis). Some of such cases are due to spinal cord

lesions causing paralysis of the bladder. Neuromuscular imbalance has been postulated as a possible explanation for others.

With distention of the renal pelvis, the calices flatten, the renal tissue becomes atrophic and thin, and the dilated pelvis assumes a saccular and rounded form. In severe cases the total size of the kidney and pelvis may be increased, and the outer surface lobulated. The atrophy and fibrosis of the renal parenchyma affect tubules more rapidly than glomeruli. Hence, except in late stages, the tubular atrophy may seem to be out of proportion to the glomerular change. Eventually glomeruli become hyalinized. The occurrence of infection converts the condition into pyonephrosis. When hydronephrosis is unilateral, the opposite kidney may undergo a compensatory hypertrophy.



Fig. 137.—Hydronephrotic atrophy of kidney. Full thickness of renal substance, with pelvic mucosa evident at the right.

The Kidney in Toxemias of Pregnancy

Renal lesions regularly accompany the toxemias of late pregnancy (eclampsia, pre-eclampsia, etc.). They are more constant and characteristic than the hepatic lesions (see p. 384). The glomeruli are enlarged, bloodless, and have narrowed capillaries. Most of the capillary narrowing is accounted for by marked thickening of the basement membrane of the tufts. Tubular changes are constantly present and often are more prominent than glomerular lesions. The con-

voluted tubules particularly are involved by changes which vary from mild cloudy swelling or fatty degeneration to hyaline droplet degeneration and even necrosis. The tubular changes, although more striking, are probably secondary and of less real importance than the glomerular lesions.



Fig. 138.—Glomerulus in eclampsia. Stained with azocarmine to show the thickened basement membrane. (From Dieckmann, William J.: *The Toxemias of Pregnancy*, St. Louis, the C. V. Mosby Company, 1941.)

In some cases of pregnancy toxemia the renal changes are those of primary glomerulonephritis, pyelonephritis, or hypertensive arteriolar nephrosclerosis. More than half of the women who recover from eclampsia eventually develop hyper-

tensive cardiovascular renal disease. The rare bilateral renal cortical necrosis also may occur in association with pregnancy (see p. 295).

Hemoglobinuria

The effects of free extracorpuseular hemoglobin circulating in the blood stream are seen following the transfusion of incompatible blood, in the complication of malaria known as blackwater fever, and to a milder degree in paroxysmal hemoglobinuria. The kidney may be so severely damaged that oliguria or anuria results, with death from renal failure.

The effects on the kidney are of two types: first, a degenerative change of convoluted tubular epithelium, varying from mild albuminous degeneration to actual necrosis; and second, the formation of casts of precipitated pigment (hematin) which block the tubules, particularly in their collecting portions. This formation of pigment casts occurs only when the urine is acid, and hence the importance of alkalization of the urine when transfusions are given, or in treatment of blackwater fever.

An entirely similar renal lesion, producing "traumatic anuria," has been described following "crush injuries." The condition has been seen in air-raid victims suffering from extensive crushing injuries of the limbs. There is marked renal tubular damage, and myohemoglobin-pigmented casts are found in the distal convoluted tubules and the collecting tubules.^{41, 42}

Tuberculosis of the Kidney

Renal tuberculosis is secondary to an active tuberculous lesion elsewhere, the organisms reaching the kidney by hematogenous spread. The kidneys are usually involved along with other organs in acute miliary tuberculosis, but another form of renal tuberculosis also occurs, in which there is a chronic ulcerative and spreading lesion. This form is usually unilateral, and the primary focus from which spread occurred often is not prominent. Embolic masses of organisms arrested in the kidney produce the first lesion in the cortex. By discharge of this lesion into a tubule, spread occurs to the medulla, where a caseous ulcerative tubercle appears on a renal papilla. From there spread occurs to the mucosa of the pelvis, ureter, and bladder. Reinfection and extension to other portions of the kidney readily follow. Tuberculous strictures of the ureter and individual calices lead to stasis of

urine and hydronephrotic changes. There is progression of the tuberculous process in the kidney tissue with caseation, loss of tissue through ulceration, and hydronephrosis.

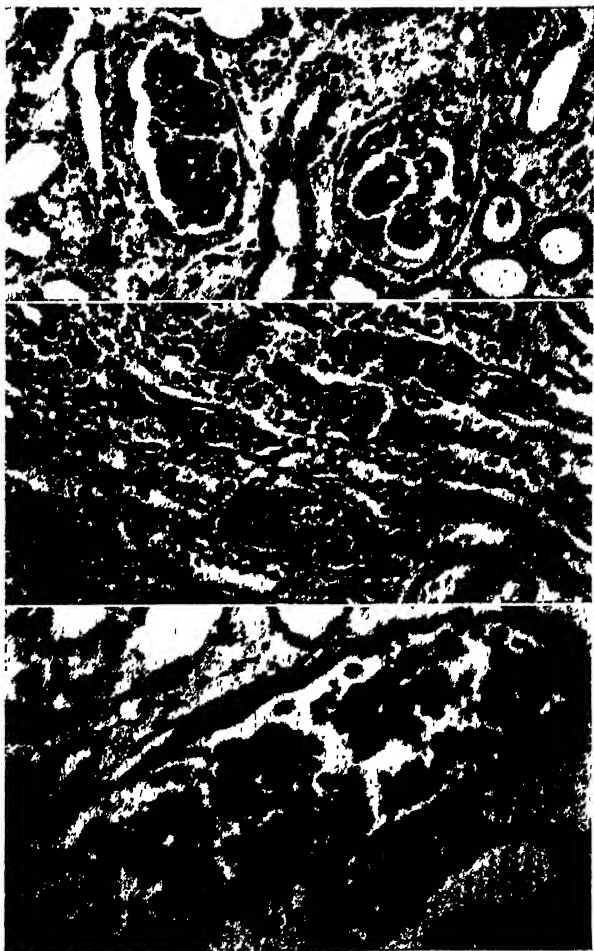


Fig. 139.—Transfusion reaction in kidney. The tubules contain pigment casts, and their epithelial lining cells show degenerative changes.

The appearance of the kidney depends upon the stage of the process. In an early period a few yellowish opaque tubercles are seen in the cortex and near the tip of a papilla. Later,

caseous masses of varying size replace the renal tissue, and the ragged hydronephrotic cavities contain a thick creamy pus.

The infected ureter becomes thick-walled, rigid, and stenosed. The urinary bladder involvement begins at the ureteral opening and spreads as an irregular area of ulceration. The lesions of the ureter and bladder tend to heal if the infected kidney is removed.

Renal Damage Due to Sulfonamides

Sulfonamide drug therapy may result in two types of injury to the kidney: (1) precipitated sulfonamide and acetylated derivatives, causing mechanical obstruction in the urinary tract, and (2) "nephrotoxic" lesions. The latter are focal or diffuse tubular degenerations and necroses, with intense inflammatory reactions. Administration of urea has prevented the precipitation of sulfonamides in the urinary tract in experimental animals.⁴³ The nephrotoxic lesions appear to be independent of the amount of drug administered and of mechanical blocking by precipitates,⁴⁴ and may have an allergic basis (see p. 185).

Congenital Malformations and Anomalies of the Kidney

Congenital absence or aplasia of both kidneys is rare and incompatible with life. Absence or aplasia of one kidney is more common, and the opposite kidney is larger than normal.

Congenital fusion of the kidneys is most commonly a connection of the lower poles, either by a fibrous band or by actual renal tissue (**horseshoe kidneys**). The pelves are separate, and the ureters pass anteriorly across the lower poles of the kidneys.

Duplication of ureters, **double pelvis**, or both, are common anomalies, usually of no functional significance. Persistence of some degree of fetal lobulation of the kidneys is also very common and harmless.

Cysts of the Kidney

Cysts of the kidney are of three main types: **solitary cysts**, **retention cysts**, due to tubular dilatation in vascular or inflammatory disease of the kidney, and the condition of **congenital polycystic kidneys**.

The solitary cysts are usually serous, but they may be hemorrhagic. They vary from a few millimeters to several

centimeters in diameter. Some are congenital in origin and others result from tubular obstruction. Occasionally they are multilocular.

In advanced renal vascular disease or glomerulonephritis there frequently are multiple small cysts, usually only a few millimeters in diameter, resulting from tubular dilatation.

Congenital Cystic Kidneys.—Congenital polycystic kidney is an hereditary maldevelopment. One or both kidneys may be involved by extremely numerous cysts, of varying and often large size. The condition is present at birth, and absence of sufficient functioning renal tissue may result in death at that time or within the next few years. If renal



Fig. 140.—Horseshoe kidneys. (Courtesy Dr. H. C. Schmeisser.)

functional tissue is sufficient, life may go on with little or no clinical evidence of the disease until the third, fourth, or fifth decade. At that time renal failure results from the development of vascular disease, other accumulated injuries of the kidney, or progressive increase in the size of the cysts. The patient may have lumbar pain, tumor mass in the kidney region, and hematuria, a picture simulating renal neoplasm. Other cases simply present acute or chronic renal failure, with mild hypertension and cardiac hypertrophy, so that clinical differentiation from other types of renal disease may be very difficult. Attacks of hematuria are a quite distinctive finding and are due to rupture of blood vessels into cysts communicating with the pelvis.

The involved kidneys may be moderately or enormously enlarged. Enlargement is due to increase in size of individual cysts, rather than to increase in their number. The kidneys have a knobby or irregular outline. The cysts are lined by cuboidal or (more commonly) flattened epithelium. In the newborn group the remaining renal tissue is hypoplastic, the number of nephrons being reduced and interstitial connective tissue excessive.



Fig. 141.—Solitary cyst of kidney. (Courtesy Dr. H. C. Schmeisser.)

At a later age, in cases without clinical symptoms, the functional renal tissue between cysts is often abundant. The patients dying of renal failure show extreme atrophy of the



Fig. 142.—Congenital cystic kidney, newborn infant. The lower figure shows a low magnification of the cut surface.

renal tissue between cysts, due to progressive cystic enlargement and associated development of arterial disease.

The origin of the condition is related to the manner of embryologic formation of the kidney. The kidney is developed from two separate portions which must join. The one portion, from metanephric blastema, forms convoluted tubules and glomeruli. The other portion, from the Wolffian duct, forms ureter, renal pelvis, and collecting tubules.

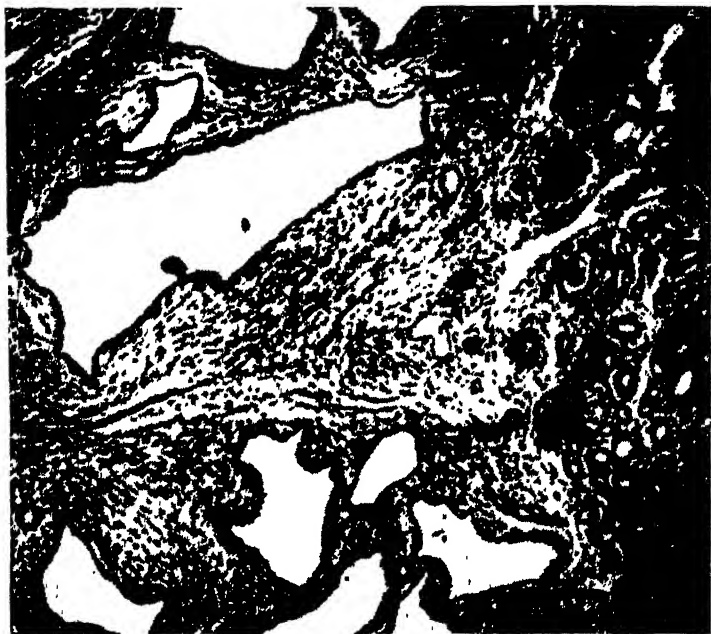


Fig. 143.—Congenital cystic kidney. Cystic spaces are surrounded by an embryonic type of connective tissue. Glomeruli and tubules are evident on the right.

“Failure of union” of collecting ducts with convoluted tubules has long been supposed to give rise to the cystic change. Kampmeier⁴⁵ has pointed out another possible origin. He showed that the uriniferous tubules, particularly of the first but sometimes of later generations, fail to gain reattachment to collecting ducts. They then undergo cystic dilatation but later normally disappear. If instead of disappearing they continue to grow and expand, polycystic kidney results.

Other abnormalities of the genitourinary tract or congenital cysts of liver or pancreas are often present in individuals with polycystic kidneys.

Renal Tumors

A. Benign.—Adenoma and fibroma are quite common but remain small and are of little practical importance. Lipoma of the kidney occurs rarely, and may grow to large size or undergo malignant change.

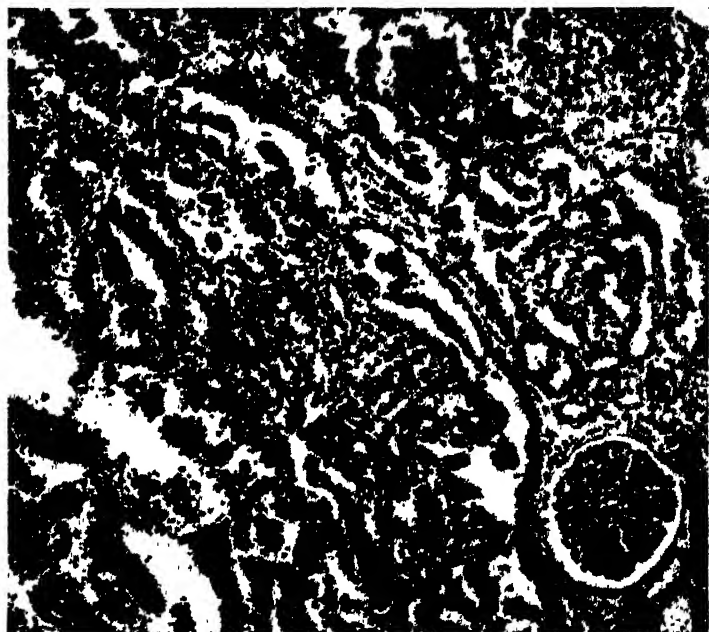


Fig. 144.—Benign adenoma of kidney. The edge of the tumor is shown, with glomeruli of the adjacent renal tissue evident on the right.

Adenoma of the kidney is commonly seen as a small grayish nodule in the cortex. Microscopically, it is composed of dark-staining epithelial cells forming well-differentiated tubules, and sometimes structures resembling glomeruli.

Fibroma is commonly found in the medulla where it appears as a tiny grayish area. It is composed of irregularly

arranged connective tissue fibers. The margin is usually irregular or ill defined, and a few tubules are often enclosed in the tumor.



Fig. 145.—Fibroma in medulla of kidney.

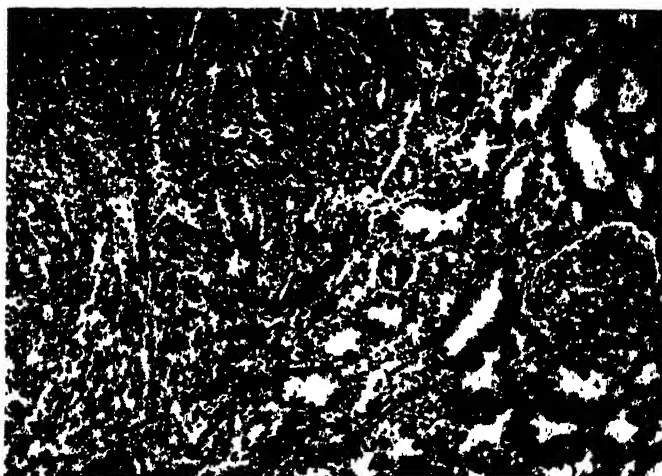


Fig. 146.—Fibroma of kidney. The edge of the tumor is shown, with tubules and a glomerulus on the right.

B. Malignant.—Malignant renal tumors are rare but of unusual interest. They are of two main types, (1) renal carcinoma or hypernephroma (Grawitz tumor) which occurs particularly in the fifth and sixth decades, and (2) the

embryonal adenosarcoma (Wilms' tumor), occurring in infancy and early childhood.

HYPERNEPHROMA (Grawitz Tumor).—Hypernephroma is the common malignant renal tumor of adults. It is called "hypernephroma" because it has been supposed to arise from "rests" of adrenal cells in the kidney. Small areas of adrenal



Fig. 147.—Hypernephroma of kidney. Some remaining renal tissue is evident in the upper portion of the figure. (Courtesy Dr. H. C. Schmeisser.)

cortical tissue are often found in the outer part of the kidney, just beneath the capsule.⁴⁶ Adrenal heterotopia, with all or part of the adrenals within the capsule of the kidneys, is sometimes encountered.⁴⁷ Also adrenal tissue is not uncommon on the under surface of the liver and in internal

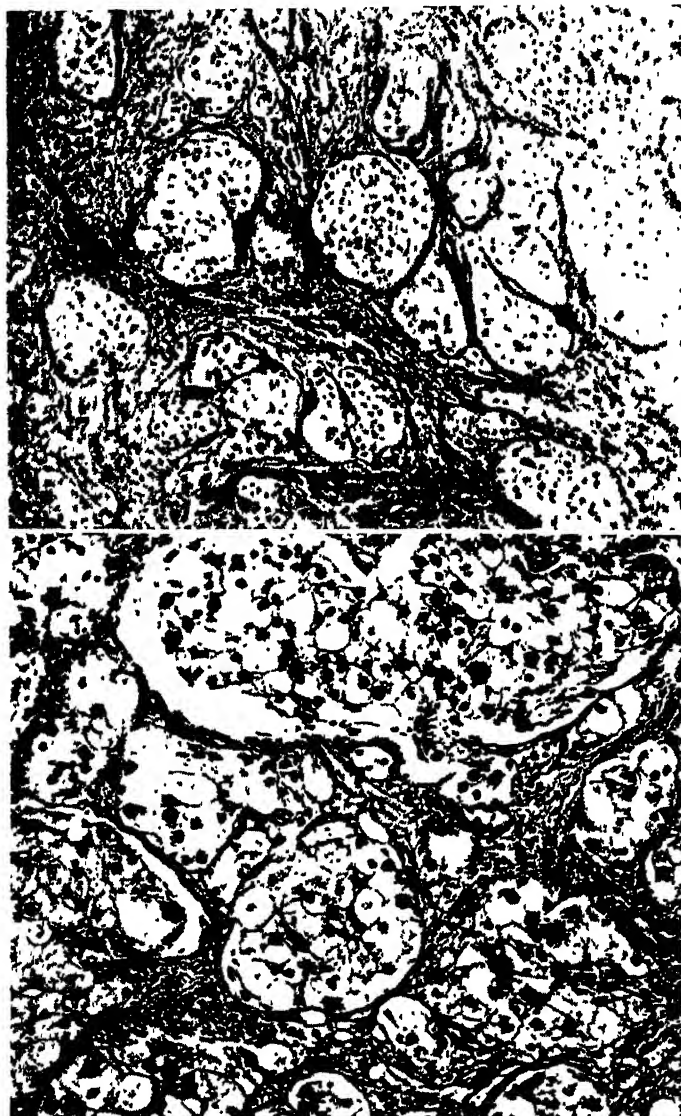


Fig. 148.—Hypernephroma of kidney. Note the nests of cells with abundant clear or foamy cytoplasm.

genitalia. Further evidence of the adrenal nature of these tumors lies in their close microscopic resemblance to adrenal cortex. They are composed of large clear cells containing abundant doubly refractive cholesterol esters, and the cells may be arranged in cords as in the adrenal cortex. However, this evidence is insufficient proof of their adrenal origin. Hypernephromas never give rise to the endocrine and sexual disturbances that accompany true adrenal cortical tumors. Some areas of the tumor may show a papillary or tubular structure, and all gradations may be found between a close resemblance to adrenal cortex, and clear-cut renal carcinoma. Hence hypernephromas are generally considered to



Fig. 149.—Wilms' tumor of kidney. Note that in this relatively early stage it appears well encapsulated and sharply separated from the renal tissue. (Courtesy Dr. H. C. Schmeisser.)

be simply renal carcinomas. However, attempts have been made to reconcile the evidences of adrenal and renal origins by suggesting that the tumor arises from cells retaining early embryonic potentialities for differentiation into either type of tissue.⁴⁸

The hypernephroma forms a large rounded tumor in the kidney, at first well encapsulated and separated from the renal tissue. It is microscopically invasive, however, so that it is not easily shelled out or separated from surrounding tissue. The yellowish cut surface shows some connective tissue trabeculae coursing irregularly through the tumor.

There is a marked tendency to degeneration, necrosis, hemorrhage, and cyst formation. Microscopically, the characteristic cells are large, with abundant, pale, foamy cytoplasm. In some areas the cells may be smaller, with a denser, slightly granular and more eosinophilic cytoplasm, more like ordinary renal tubular epithelium. The cells are arranged in solid sheets, or as cords and papillary structures with a thin supporting stroma.

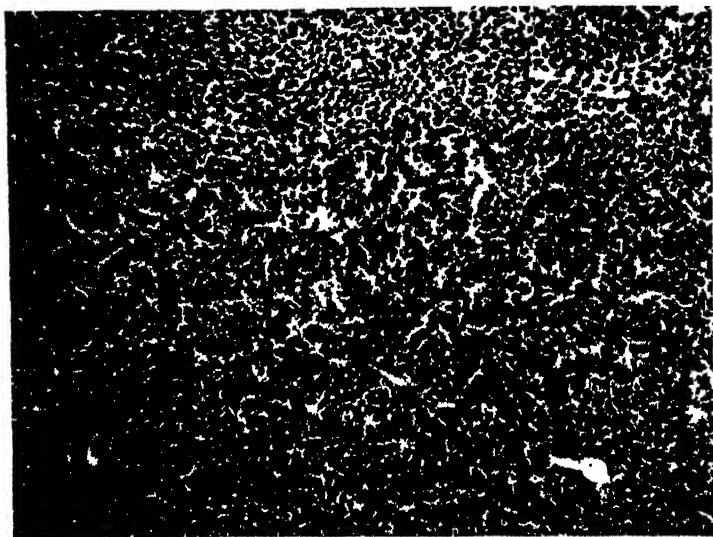


Fig. 150.—Wilms' tumor of kidney. Note the tubular or rosette-like structures amidst the general sarcomatous appearance.

The growth of the tumor causes atrophy and fibrosis of adjacent tissue. In later stages there is extensive invasion of renal substance. The tumor cells have a tendency to invade and grow along blood vessels. Metastasis occurs by blood stream, and the lungs and bones are the common sites for the secondary tumors.

Because of the relatively localized growth of hypernephroma in its early stages, it may attain considerable size with only painless hematuria as clinical evidence of its presence. Metastases in lungs or bones may be the first indication.

EMBRYONAL ADENOSARCOMA (Wilms' Tumor).—Embryoma is a rare mixed tumor of the kidney, the occurrence of which

is practically limited to the first seven years of life, although a few cases have been reported in adults. The average age is three years. These tumors account for about 20 per cent of all malignancies in childhood. The origin is believed to be from mesodermal cells displaced during development but retaining the ability to grow and differentiate into various types of tissue. Being rapidly growing tumors of embryonic nature, they are highly radiosensitive.



Fig. 151.—Papillary carcinoma of renal pelvis. (Courtesy Dr. H. C. Schmeisser.)

At first the tumor is surrounded by a dense connective tissue capsule and remains separated from the renal parenchyma until quite large. The kidney tissue is pushed into various shapes. Eventually the capsule is ruptured and extension occurs to kidney tissue, omentum, and adjacent

viscera. Blood-borne metastases are common in lungs and brain, but liver and regional lymph nodes are also frequently involved.

The tumor tissue is uniformly grayish white and moderately firm, but cysts or hemorrhage may be present. Microscopically, the predominant tumor elements are an abundant embryonic type of malignant connective tissue surrounding

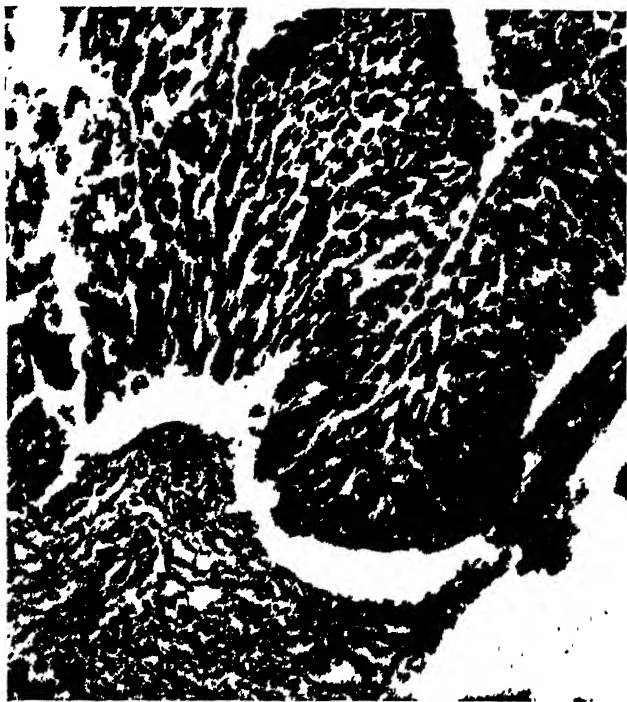


Fig. 152.—Papillary carcinoma of renal pelvis. (Microscopic section of tumor in Fig. 151.)

some gland-like tubules of variable size and shape. Epithelial cells may also form solid cords and strands of cells. Occasionally smooth or striated muscle, cartilage or myxomatous tissue is present.⁴⁹

SARCOMA.—Sarcoma may arise from connective tissue of the kidney, but this is uncommon.

Tumors of the Renal Pelvis.—The pelvis of the kidney gives rise to the same types of tumor as are found in the

bladder, the common forms being papilloma and papillary carcinoma. An infrequent variety is squamous-cell carcinoma.



Fig. 153.—Multiple strictures of ureter, with hydronephrosis. (Courtesy Dr. H. C. Schmeisser.)

URETER

The most important pathologic involvement of the ureters is obstruction, which may be by a calculus from the renal pelvis, a fibrous stricture resulting from inflammation, or less frequently due to tumors, either of the ureter itself or adjacent to and pressing on the ureter. Kinking of the ureter when the kidney is abnormally movable or an aberrant renal artery crossing the ureter causes some cases of partial or intermittent obstruction. Hydronephrosis is the common result unless the obstruction is transitory. Obstruc-

tion of the urinary tract below the ureters causes bilateral dilatation of the ureters (hydroureter).

Tumors of the ureter are uncommon and are of the same gross and histologic types as those which arise in the bladder.

URINARY BLADDER

Inflammation, obstruction, and tumors are the important lesions of the bladder; congenital abnormalities and traumatic changes are less common.

Inflammation.—Inflammation of the bladder (cystitis) may be acute or chronic. The infection may descend from a pyelonephritis, may reach the bladder by way of the urethra, or be introduced by catheterization. Obstruction of the bladder outlet, as by a calculus or enlarged prostate, is particularly apt to be associated with chronic inflammation. Important organisms in cystitis are pyogenic cocci and the colon bacillus.

In acute cystitis the mucosa is congested, edematous, and may be hemorrhagic or ulcerated. Congestion and inflammatory cells, particularly in submucosa, are evident microscopically.

Chronic cystitis is associated with considerable thickening of the bladder wall by granulation tissue and fibrosis, unless an associated obstruction causes the wall to be dilated. Occasionally the thickened mucosa shows small, fluid-filled cystic cavities, the so-called *cystitis cystica*.

Interstitial cystitis, occurring predominantly in women, is a chronic inflammation in the subepithelial and intermuscular connective tissue.

Obstruction.—Obstruction to the outlet of the urinary bladder may be caused by prostatic hypertrophy, stenosis following urethritis, tumor, calculus, or neurogenic disturbance. The bladder becomes distended and thin walled. Hypertrophy of muscle bundles follows if the obstruction is prolonged, so that the inner surface of the distended bladder is roughened by prominent muscular trabeculae. Distention of weak areas between the trabeculae may produce multiple small (false) diverticulae.

Tumors.—Tumors of the urinary bladder are more frequent in men and commonly occur in the age group of 50 to 70 years. Etiologic factors are not apparent in most instances. Aniline dye workers excreting the dyes in the urine show a high incidence. The base or trigonal region of the bladder is the favorite site.

The common types are: (1) papilloma, (2) papillary carcinoma, (3) transitional cell carcinoma. Various other varieties occur but rarely, including adenocarcinoma and mucoid carcinoma.



Fig. 154.—Chronic cystitis and hypertrophy of bladder. Diverticulum of bladder (opening indicated by small rod). Prostatic calculi. (Courtesy Dr. H. C. Schmeisser.)

The **papilloma** is a delicate pedunculated tumor projecting from the mucosal surface. It has a narrow base and many fine villous processes. Delicate branching villi com-

pose the tumor, each having a thin connective tissue core containing blood vessels, separated by a definite basal membrane from a surface covering of transitional epithelial cells. The epithelial cells are uniform in size, shape, and staining.

Papillomas are frequently multiple and tend to recur. They are always potentially malignant, though they may remain benign for months or years. Evidence of malignancy is most apt to be invasion at the base of the pedicle, so that a section through this area is most important in diagnosis. Other findings suggesting malignancy are a breaking through of the basal membrane separating the stromal core, a growing together of the villi, and atypical staining and morphology of the epithelial cells.

Papillary carcinomas have a general architecture similar to that of the benign papillomas. They are more frequently single, firmer, have a broader base, and form large, bulky, cauliflower-like growths with a tendency to hemorrhage and necrosis. There is more irregularity of arrangement, size, and shape of the epithelial cells, and mitoses are more numerous than in papillomas. The processes tend to be fused, and there is invasion of the connective tissue stroma or of the wall of the bladder from the base of the tumor.

Transitional cell carcinoma forms a sessile infiltrating type of tumor which spreads widely through the bladder wall and to surrounding structures, though no large tumor may form in the bladder lumen. Necrosis and ulceration tend to occur. A few of these infiltrating tumors are composed of squamous rather than transitional epithelial cells.

Spread of bladder cancer is usually late and not very extensive, particularly in the papillary forms of low malignancy. Invasion of surrounding structures and metastasis to pelvic and prevertebral lymph nodes usually precede spread to lungs, liver, or bones.

MALE GENITAL ORGANS

Penis.—Phimosis is a condition in which the foreskin cannot be retracted. In **paraphimosis**, a retracted foreskin cannot be brought forward. These conditions may be congenital, or acquired and due to inflammatory swelling and edema. **Balanitis** is an inflammation of the glans. It is predisposed to by phimosis. The gonococcus and the colon bacillus are the common causative organisms.

The venereal lesions which may affect the penis are chancre, syphilis (chancre), lymphopathia venereum, and granuloma inguinale. They have been considered in Chap. VII.

Squamous-cell carcinoma is the only important tumor of the penis. It occurs on the glans or prepuce (less commonly), usually after 50 years of age, and often it is preceded by chronic irritation from balanitis, phimosis, or uncleanliness. It begins as a small warty growth, later developing into an ulcerative fungating mass. Metastasis occurs to inguinal and, later, to retroperitoneal nodes.

Urethra.—Inflammation (urethritis) is the common lesion of the urethra and is usually of gonorrheal origin. It is accompanied by abundant pus production and much desquamation of epithelium.

Stricture of the urethra is a common end result of gonorrhea, but its origin also may be traumatic or due to a congenital fold of mucosa. The obstruction may cause dilatation of bladder, ureters, and renal pelvices.

Testis and Epididymis.—**Varicocele** is a varicose dilatation of the veins of the spermatic cord. **Hydrocele** is the accumulation of clear watery fluid in the tunica vaginalis. If blood is present, it is referred to as a **hematocele**. **Spermatocele** is a dilatation of the duct of the epididymis.

Inflammation (epididymitis) is most commonly due to gonorrhea, the infection usually spreading from seminal vesicles. One finds suppuration and the formation of small abscesses. Scarring which follows the inflammation often prevents passage of spermatozoa, thus causing sterility, though testicular atrophy and sexual inactivity do not necessarily result. Nongonorrheal epididymitis is less common but may result from staphylococcic or colon bacillus infections.

Acute orchitis (inflammation of the testicle) may result from trauma or complicate certain infectious diseases, particularly mumps, typhoid fever, and smallpox. It is the most serious feature of mumps in young adults. In some cases it is followed by testicular atrophy and sterility.

Tuberculosis may involve the epididymis before other parts of the urogenital system. Small conglomerate caseous tubercles are formed, similar in their gross and microscopic appearance to tubercles elsewhere. **Syphilis** more commonly involves the testis first and the epididymis secondarily. The syphilitic orchitis may be a gumma or a diffuse fibrosis.

Hyalinization of seminiferous tubules has been found associated with hypogonadism and testicular failure. A progressive sclerosis beginning in the basement membranes and tunica propria of the tubules results in hyalinization, with disappearance of germinal and Sertoli cells, and an ap-

parent increase and clumping of Leydig cells. Azoospermia and high urinary gonadotropins are associated with this lesion.⁵⁷

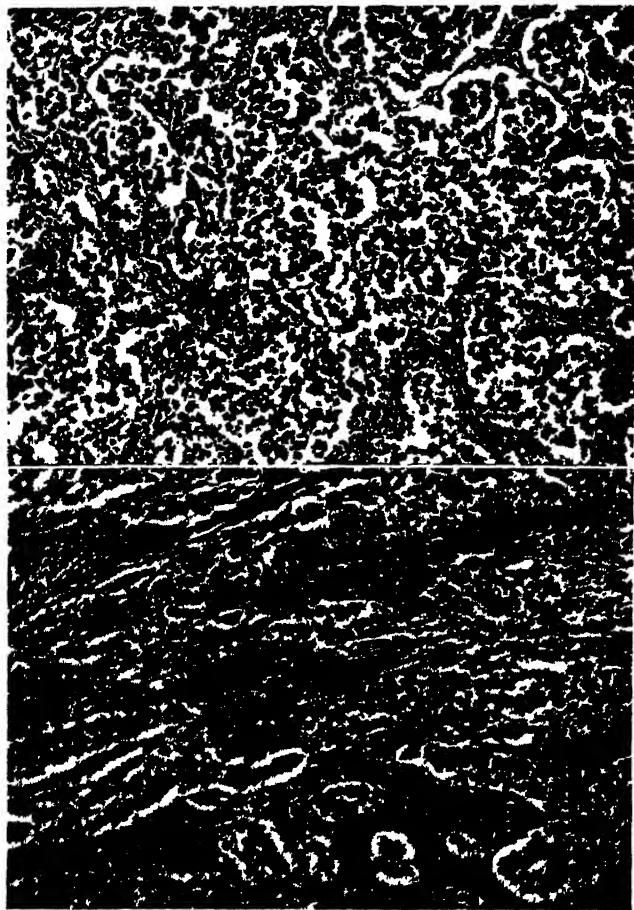


Fig. 155.—Seminoma of testis. Cords of tumor cells with large round dark nuclei are separated by a fibrous stroma infiltrated with lymphocytes.

Cryptorchism is a failure of descent of the testis into the scrotum. The testis is found in the peritoneal cavity or in the inguinal canal. The condition may be unilateral or bi-

lateral. Undescended testicles are usually deficient in spermatogenesis, but they do produce the hormone necessary for secondary sexual characteristics. Malignant tumors are much more frequent in the cryptorchid than in the normally descended testis.

Tumors of the Testis.—Almost all testicular tumors are malignant and account for about 0.6 per cent of cancer in males. In 11 per cent of cases there is an associated cryptorchism or ectopic position of the testis.⁵² Most testicular tumors occur between 20 and 45 years of age. The classification and terminology of testicular cancers are variable and confused. Ewing has regarded them all as teratomas, arising from sex cells and capable of reproducing any tissue. Commonly they are divided into two groups, seminomas and teratomas.

SEMINOMA.—The seminoma (disgerminoma, spermatocytoma, embryonal carcinoma) is a firm, fleshy grayish-white mass, sharply circumscribed, and varying up to the size of a grapefruit. Histologically, it is composed of rounded or polygonal cells with prominent round or oval hyperchromatic nuclei, arranged in diffuse sheets or in a pseudopapillary form. A scanty stroma separates groups of cells and is often infiltrated with small lymphocytes. This microscopic appearance is similar to that of disgerminoma of the ovary (see p. 571), but it is much more malignant than the ovarian counterpart.

TERATOMA AND MIXED TUMORS.—Included in this group are adult or differentiated teratomatous tumors containing various types of tissue, and also more highly malignant varieties in which only one type of cell is found. The gross appearance is as variable as its microscopic composition. A large size is often attained, and cyst formation is common. Microscopically, undifferentiated and unrecognizable highly malignant tumor cells may be found, or differentiated structures such as cartilage, muscle, fat, glands, myxomatous tissue, etc. A rare and peculiar type is a chorionepithelioma, similar to the tumor which occurs in the uterus (see p. 595).

Most malignant testicular tumors are associated with production of pituitary-like hormones, and a positive Aschheim-Zondek test is obtainable. On a quantitative basis, the test shows some correlation with histologic type, though not close or very reliable.⁵³ The adult type of teratoma has a low level of hormones, the seminoma higher, and the chorionepithelioma very high.⁵⁴

Most of the testicular malignancies are highly radiosensitive. The well-differentiated tumors or adult types of teratoma respond least. Metastasis occurs by blood and lymph channels. Lymphatic metastasis is found most frequently in



Fig. 156.—Teratoma of testis. Note the variety of cells and structures.

the pelvis and abdominal retroperitoneal nodes. The lungs and liver are the organs most often the site of metastases.

INTERSTITIAL CELL TUMORS.—The interstitial (Leydig) cells of the testis are numerous in adults and appear increased in

atrophic testes, as in elderly individuals or in undescended testes. Benign tumors composed of mature interstitial cells are of rare occurrence and have an endocrine function. In

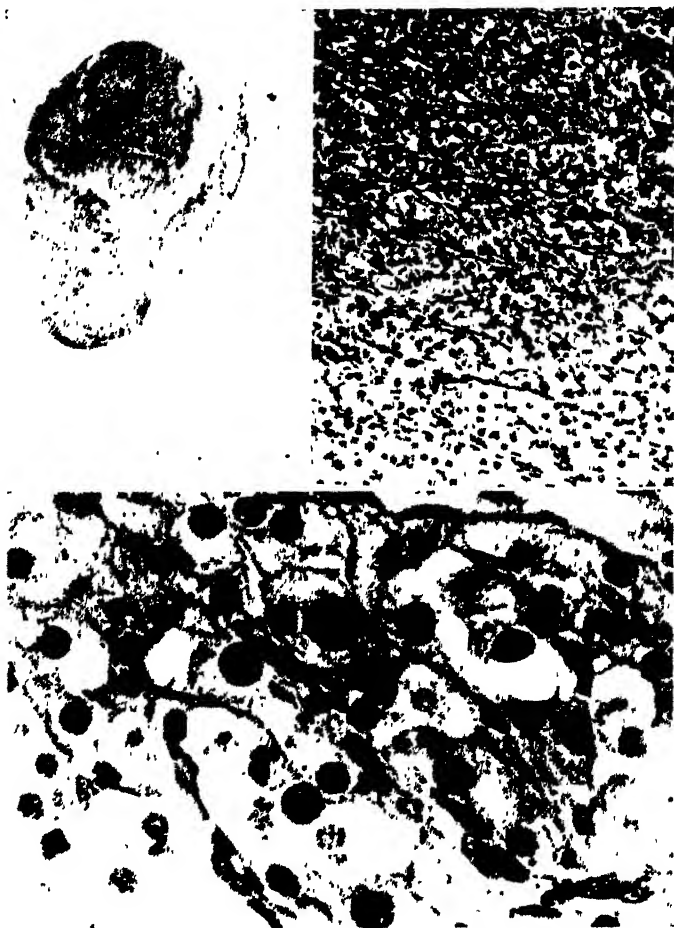


Fig. 157.—Interstitial cell tumor of testis. From a boy aged 7 years, with hypergenitalism.

children, it is a rare cause of hypergenitalism and precocious development of secondary sexual characteristics.⁵⁵

Prostate.—The prostate is a sexual gland, its secretion being mixed with the sperm in the urethra at the time of

ejaculation, and functioning to activate and prolong the motility of the spermatozoa. The gland has five lobes (median, two lateral, posterior, and anterior), and a group of gland acini in the midline of the urethral floor between the posterior vesical lip and the verumontanum (the subcervical urethral glands of Albarran). The median lobe is that part dorsal to the urethra and between the converging ejaculatory ducts. The median lobe, the glands of Albarran, and the lateral lobes are particularly prone to undergo benign enlargement and cause obstruction.

The prostatic glands are lined by cuboidal or cylindrical epithelium and often contain concentrically laminated concretions, corpora amylacea. A hormonal secretion of the testis, activated in turn by the pituitary, influences the prostate and causes its rapid maturation at puberty. Involution progresses during and after the fifth decade, due to decrease of hormonal stimulation.⁵⁶



Fig. 158.—Corpora amylacea of prostate.

The important lesions of the prostate are inflammation, benign enlargement, and carcinoma.

INFLAMMATION.—**Acute prostatitis** is most common as a complication of gonorrhea. The purulent material is confined within acini or extends and forms abscesses. The inflammation may clear up, but commonly becomes chronic. Septicemias and pyemias also may result in multiple small abscesses of the prostate, the *Staphylococcus aureus* being the most common organism.



Fig. 159.—Nodular hyperplasia of prostate. The enlarged median lobe of the prostate projects upward into the bladder. The inner surface of the dilated bladder is trabeculated. (Courtesy Dr. H. C. Schmeisser.)

Tuberculosis is common in the prostate, usually carried there by the blood stream, and in less than 20 per cent of cases it is secondary to foci elsewhere in urogenital organs.⁵⁷ Typically caseous lesions are formed, similar to tuberculosis elsewhere.

NODULAR HYPERPLASIA (Benign Prostatic Hypertrophy).— Benign enlargement is the commonest lesion of the prostate, being found in about 30 per cent of men over sixty. About 17 per cent have symptoms of urinary obstruction as a result, this being its main and important effect. The enlargement possibly is due to some imbalance of hormonal control.

The **anatomic changes** are the result of hyperplasia in the lateral lobes, the median lobe, or the subcervical glands of Albarran. The earliest change is usually a proliferation of periductal, periacinar, and periurethral stroma, relatively rich in smooth muscle fibers but deficient in elastic tissue. Hyperplastic glandular growth usually occurs as a secondary phenomenon. Localized nodules of tumor-like or adenomatous tissue result, in which there are cystic dilatations of acini with papillary infoldings lined by a single layer of high columnar epithelium, and also areas with increase in number of acini. Occasionally there are nodules composed only of smooth muscle, or masses of lymphoid tissue.

The **effect of prostatic enlargement** is to obstruct the outflow of urine. Enlargement of the lateral lobes compresses the urethra into a narrow and irregular slit. Enlargement of the median lobe or of the subcervical glands of Albarran results in a nodular mass which pushes up the floor of the bladder just inside the sphincter or in the proximal part of the urethra. This midline enlargement is particularly effective in obstructing outflow of urine, acting as a plug to close the urethral orifice. A small sac forms behind the prostatic nodule, from which urine cannot be expelled, and contains the so-called residual urine.⁶⁰

Results of the obstruction may be seen in all parts of the urinary tract proximal to the prostate. The bladder becomes hypertrophied, with prominent muscular trabeculation evident on its mucosal surface. Diverticula may develop in weak areas between the trabeculae. The ureters and renal pelvices undergo dilatation (hydroureter and hydronephrosis).

The **etiology** has been variously considered to be chronic inflammation, arteriosclerosis, and hormonal imbalance. The concept that the condition is one of true tumor formation has been rejected, and the nodular hyperplasia is thought to be a response to excessive stimulation by a hormone from

the interstitial cells of the testes. Hormone production by the testis is itself under the control of gonadotropic principles of the pituitary.⁶¹

CARCINOMA.—Carcinoma of the prostate occurs with increasing frequency after the fourth decade, being found in 14 to 29 per cent of males examined at autopsy in the older age groups.⁶² In a large proportion of these cases the cancer is occult and has given rise to no clinical manifestations. Its occurrence is associated with senile atrophy of the gland, but it is quite independent of the condition of benign enlargement. The posterior lobe is most often affected, but it may arise in any part of the gland. Acid phosphatase of the serum is usually increased in patients with carcinoma of the prostate. If there are skeletal metastases, the alkaline phosphatase also may be increased.

The carcinomatous prostate tends to be firm or hard, and lacking the elastic consistency of benign enlargement. With invasion through the capsule, the prostate becomes fixed to surrounding structures. Microscopically, there are numerous acini which tend to be irregular and lined by several layers of epithelium, and also solid cords of epithelial cells irregularly invading adjacent tissue. Invasion of the capsular perineural lymphatics occurs early. More distant lymphatic spread to the pelvic nodes is a late occurrence. Hematogenous metastasis to bone is common, where an osteoplastic reaction is induced by the tumor cells. (See p. 666.) Treatment by castration or with stilbestrol causes degenerative and atrophic changes in the tumor cells.

SARCOMA.—Sarcoma of the prostate is rare and easily confused with anaplastic carcinoma. Myosarcoma appears to be the most frequent type, but lymphosarcoma, spindle-cell sarcoma, and other forms also occur.

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CHAPTER XIV

THE LUNGS

BRONCHI

The bronchi are involved in four main types of lesions: inflammation (bronchitis), obstructions (bronchial asthma), dilatations (bronchiectasis), and tumors (bronchogenic carcinoma). These types are frequently mixed, e.g., bronchiectasis and asthma have inflammatory changes as an integral part of the picture, and bronchogenic carcinoma may be associated with obstruction of the bronchial lumen.

Inflammation

Acute Bronchitis.—Acute bronchial inflammations have a varied etiology, and a number of organisms may be found in the associated exudate. In many cases the trachea and larynx are involved as well, so that the condition is a laryngotracheobronchitis. Influenza is primarily a tracheobronchitis. Downward extension of diphtheria produces a fibrinous bronchitis. Pneumonic involvement of lung has an associated acute bronchitis.

In acute bronchitis the mucosa is thickened, reddened, and eventually covered by exudate which may be mucoid, fibrinous, or purulent. Microscopically one finds congestion and infiltration of mucosa and often of deeper layers by polymorphonuclear leucocytes. In severe cases, necrosis and desquamation of the epithelial surface may be evident, blending with the exudate on the surface. Dilatation (bronchiectasis) may result from the injury to bronchial walls, or abscess formation may follow spread of the infection.

Chronic Bronchitis.—Chronic bronchial inflammation is a common condition usually associated with one of three conditions: (1) heart disease in which there is a chronic congestion of the lung; (2) infection in the upper respiratory tract, such as chronic sinusitis; (3) bronchiectasis. Less commonly it may be due to prolonged exposure to irritating dusts or gases.

The bronchial mucosa is covered with a mucoid or mucopurulent exudate and is reddened and thickened so as to obscure the normal longitudinal markings. Microscopically

one finds widespread infiltration by lymphoid cells and excess of fibrous connective tissue. The mucosal epithelium may be cubical or flattened, and the mucous glands atrophic.

Obstruction

Obstruction of a bronchial lumen can be produced by (1) aspirated foreign material, (2) neoplasms, (3) pressure from without, as by enlarged lymph nodes, (4) inflammation or its sequelae, and (5) asthma. A complete obstruction leads to collapse (atelectasis) of the lung tissue supplied by the obstructed bronchus. Incomplete obstruction, or one which allows entrance of air by active inspiration but blocks its exit on passive expiration, leads to dilatation of alveoli (emphysema). Aspiration of foreign substances into bronchi often leads to abscess of the lung.

Bronchial Asthma.—Asthma is an allergic condition characterized by dyspnea, with particular difficulty in expiration. The sensitivity may be to food, pollens, or bacterial products. However, an allergic basis is not demonstrable in all cases of asthma, and metabolic changes may be present which suggest a functional disturbance of the adrenal cortex.³ Sputum produced in asthma is often distinctive due to a content of eosinophiles, Curschmann's spirals, and Charcot-Leyden crystals. Excessive numbers of eosinophiles may be found in the blood. Asthmatic attacks are characterized by spasm of bronchial muscles and overproduction of mucus by bronchial glands. Death during an attack is uncommon.

The lungs in asthmatics are voluminous and emphysematous. Areas of atelectasis also may occur due to persistent bronchial obstruction by mucous plugs.

In the bronchiolar wall there are (1) infiltration of eosinophiles, (2) hypertrophy of muscle, (3) a thickened basement membrane and widened submucosal layer, and (4) enlargement and hyperactivity of mucous glands, which may be infiltrated by eosinophiles. Excessive mucous secretion is present in the lumen, sometimes in the form of peculiar spiral plugs (Curschmann's spirals).^{1, 2}

Bronchiectasis

Bronchiectasis is a dilatation of bronchi, either in a local area, or generalized. The dilatation may be cylindrical, fusiform, or saccular, if localized to one area. The lower lobes are more commonly involved, and the left more frequently than the right. The condition is frequently associated with

(1) chronic bronchitis or (2) multiple abscess formation due to invasion of pyogenic and fusospirochetal organisms.

Etiology.—The etiology and pathogenesis have been much debated, but a number of factors are considered causative, their relative importance varying in different cases. These factors are:

1. **Infection of the bronchial wall.** Acute respiratory infection involving the bronchial wall, particularly in children, may injure or destroy muscle and elastic tissue. This most commonly follows bronchopneumonia or bronchitis complicating whooping cough, measles, and influenza.

2. **Traction on the bronchial wall from without.** This may occur either from (a) atelectasis of lung tissue or (b) contraction of scar tissue resulting from inflammation of alveolar and bronchial tissue. Atelectasis brought about by an obstruction of the bronchial lumen exerts elastic pull on the bronchial wall because of the negative pleural pressure and the necessity for spatial adjustment in the thoracic cage. Fibrous contraction of pulmonary tissue, from tuberculosis, fibrous pneumonia, etc., similarly may exert traction tending to dilate bronchi.

3. **Increased intrabronchial pressure,** such as produced by coughing. This may act to dilate bronchi when the wall is already weakened by an inflammatory and destructive process.

4. **Congenital abnormality in bronchial development,** particularly of the muscular and elastic components. There is a congenital type of bronchiectasis, which includes the lesion referred to as congenital lung cyst. That a developmental factor may be important in the seemingly acquired cases has been suggested by the peculiar distribution of bronchiectasis, its frequent familial occurrence, and association with other developmental abnormalities.^{4, 5, 6, 7}

Lesions.—The dilated bronchi are evident on the cut surface of the bronchiectatic lung. In the lower lobes the dilations are usually cylindrical, whereas in the less commonly involved upper lobes they tend to be saccular. When inflammation is marked, particularly with pyogenic and fusospirochetal infections, the bronchiectases appear grossly as multiple abscess cavities.

Microscopically, the essential change is absence, damage, or destruction of muscular and elastic elements of the bronchial wall. This may be accompanied by variable degrees of inflammation. In slight and chronic bronchiectasis there may be either atrophy or hypertrophy of mucosa, with infiltration of lymphocytes and plasma cells in the bronchial

wall, and eventually fibrosis. Squamous metaplasia of the lining is an occasional occurrence. With severe inflammation there may be necrosis of tissue, purulent exudate, and abscess formation. A focal necrotizing pulmonary lesion or abscess in the process of healing may become lined by a wall resembling that of a dilated bronchus, so that it is often mistakenly considered as a saccular type of bronchiectasis.

Congenital Bronchiectasis and Congenital Lung Cyst.—Congenital bronchiectasis is rare, and frequently spoken of as cystic disease of the lung.⁵ Anomalous bronchial or pulmonary development results in variously sized cavities, which may or may not have an opening into a bronchus. The cyst is lined by columnar epithelium, and some remnants of muscle and cartilage may be found in the wall.

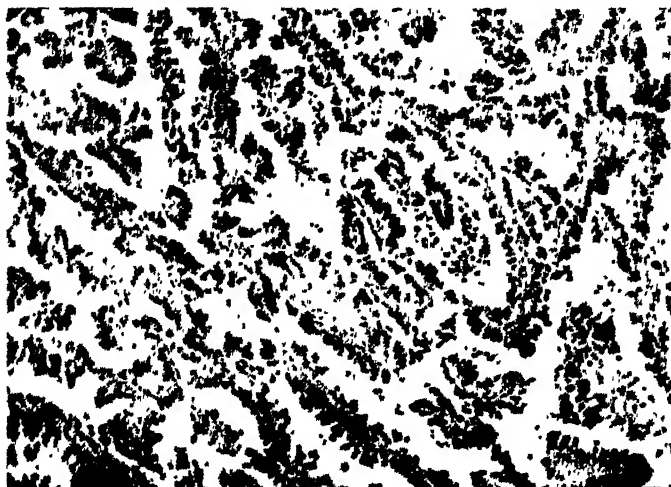


Fig. 160.—Cylindrical cell carcinoma of bronchus. The tumor has a papillary structure.

Bronchogenic Carcinoma

Primary carcinoma of the lung is of frequent and increasing occurrence. It is more common in men, and the greatest incidence is in middle life.¹¹ The etiology and the reason for its increase are unknown, but often are blamed on tarring of roads and use of tobacco. It is mainly bronchogenic in origin, arising from bronchial mucosa or glands. Grossly it may occur as a tumor mass at the hilus of the

lung, as multiple tumor nodules, or as a diffuse pulmonic spread of tumor. Microscopically, the main histologic types are squamous cell, undifferentiated (reserve cell), and columnar cell, in that order of frequency. Metastases tend to be widespread, most often involving the regional, cervical, and abdominal lymph nodes, and the liver, kidneys, adrenals, bones, and brain.

A small proportion of primary tumors of the lung are considered to arise from alveoli, rather than to be bronchogenic, and have been termed alveolar cell tumors.¹² The gross form may be multiple nodular tumors, or a diffuse involvement of one lobe or lung. The alveolar walls comprise the stroma, and are lined by cuboidal or columnar tumor cells, often with papillary protrusions into the lumen.

Incidence and Etiology.—The lung ranks as one of the commonest sites for primary carcinoma, in some autopsy series being exceeded in frequency only by the stomach. Its incidence has been increasing in recent years, though much of the increase may be apparent rather than real and due largely to better recognition of the condition and the increased span of life.^{9, 14}

As in cancer elsewhere, the exact etiology is obscure. The role played by inspired irritants, such as dust from mines, roads, and tobacco smoke, has been emphasized in recent publications.¹¹ In certain miners the incidence of bronchogenic carcinoma is very high and has been attributed to a radioactive element in the dust of the mines. Silicosis and asbestosis have been believed also to be predisposing factors.⁵⁸ The evidence that smoking may play an etiologic role has been reviewed by Ochsner and DeBailey.¹¹ Hereditary predisposition is probably important in pulmonary carcinoma, as in cancer elsewhere.

Gross Types.—While extremely variable in gross appearance, most pulmonary carcinomas fall in three groups. The most common is a **hilar infiltrating form**, in which there are large tumor masses about the bronchi at the hilus of the lung, causing stenosis and ulceration of a bronchus, and often massively involving mediastinal and peribronchial lymph nodes. In the less common **nodular form**, there are multiple nodular tumor masses scattered through the lung. A **diffuse form**, simulating a pneumonia or organizing consolidation of the lung, may be difficult to recognize grossly.

By bronchial obstruction, pulmonary carcinoma may result in abscess, pneumonia, bronchiectasis, or atelectasis. In the apex of the lung and at the thoracic inlet the tumor may

result in a distinctive clinical symptom complex, characterized by pain around the shoulder and radiating down the arm, Horner's syndrome (unilateral exophthalmos, miosis, ptosis, and anhidrosis), and atrophy of the muscles of the arm and hand. Pancoast¹³ described the lesion in such cases as a "superior pulmonary sulcus tumor." These apical tumors are apparently carcinomas of the terminal bronchioles which extend to involve the inferior cervical ganglion and the brachial plexus.

Microscopic Structure.—Carcinoma of the lung is believed to arise from mucosal and gland cells of the bronchi rather than from the alveolar lining cells. While these tumors show considerable histologic variation, they can usually be classed as squamous cell, undifferentiated, and columnar cell types.

The squamous cell type is most common and may show formation of keratin pearls and intercellular bridges. The parent (reserve) cells of bronchial epithelium are capable of differentiation into squamous cells, and squamous metaplasia of this epithelium not infrequently results from chronic inflammatory processes.

The undifferentiated group are anaplastic tumors which arise from embryonic or "reserve"¹⁵ cells of bronchial epithelium. They consist of round, spindle-shaped or oat-shaped cells, with scanty cytoplasm, deeply staining nuclei, and without any particular structural formation. Some of the undifferentiated tumors are often mistaken for sarcoma. Occasional foci of differentiation, with squamous or cylindrical cells, may be found.

The cylindrical cell carcinomas are composed of cuboidal or cylindrical epithelial cells and may be differentiated enough to form glandular or mucous structures.

The histologic form can be correlated to some extent with type of spread and prognosis.¹⁶ The squamous cell variety is relatively slow in growth, forming a bulky, locally invasive tumor often accompanied by infection and necrosis, but with relatively little tendency to metastasize. The undifferentiated type is highly malignant and has a poor prognosis. Usually arising at the hilus of the lung, it tends to invade the mediastinum and extend widely by lymphatics. The columnar cell carcinoma offers a poorer outlook than the squamous cell type, as it tends to metastasize widely by the blood stream as well as involving lymph nodes.

Metastasis.—Spread of carcinoma of the lung is by direct extension, through lymphatics, by the blood stream,

and by "bronchial embolism." Regional lymph nodes are involved in a high proportion of cases, the other common sites of metastasis being liver, adrenals, bones, brain, and kidneys. A hematogenous spread may produce very widely disseminated metastases.

Bronchial Adenoma

Polypoid bronchial adenomas form less than 10 per cent of bronchogenic tumors. They arise in the wall of a major bronchus, under its mucous membrane, and grow into and occlude the lumen. Chronic pulmonary suppuration is a common complication as a result of the bronchial obstruction.

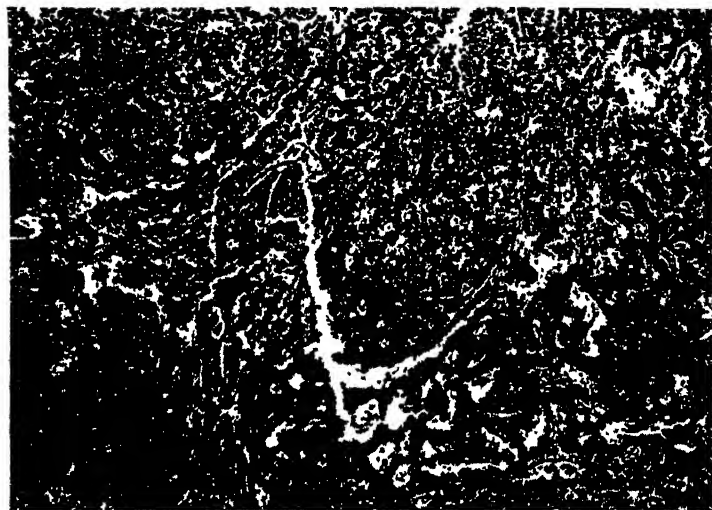


Fig. 161.—Bronchial adenoma. (Army Medical Museum, courtesy Major Arthur C. Allen.)

They tend to occur in youth or middle age, at a lower average age than bronchogenic carcinoma, and are more frequent in females. Their growth is slow, and although there may be some local invasion, metastases rarely occur. The microscopic structure is variable, but often there are cords, strands, or alveolar masses of cells with dark nuclei and scanty or clear cytoplasm, and lacking evidence of rapid growth. The stroma is variable in amount, but often highly vascular. A microscopic resemblance to carcinoid tumors of the bowel

has been pointed out. The exact cellular origin is still under discussion. While considered by some to be mixed tumors of embryonic origin,¹⁷ they are more generally considered to arise from the bronchial serous or mucous glands, and possibly from oncocytes, peculiar cells with acidophilic granules which occur among adult bronchial glands.¹⁸

Metastatic Carcinoma of Lung

The lung is a common site for metastatic tumors, spread usually being by the blood stream. Sarcomas, such as those of skin or bone, frequently produce metastases in the lungs,



Fig. 162.—Metastatic carcinoma of lung (primary in esophagus).
(Courtesy Dr. H. C. Schmeisser.)

as do also the renal tumors, hypernephroma, and embryonal adenoid sarcoma. Usually multiple discrete nodular tumor masses are produced. Occasionally a lymphatic extension to the lung may occur from cancer of the breast. A peculiar

type of tumor metastasis to the lung has been described under the terms lymphangitis carcinoma and "diffuse infiltrative carcinoma."^{20, 21} The clinically inconspicuous primary tumor is an infiltrative scirrhous carcinoma of the stomach or colon occurring in a young adult or in early middle life. Rapidly progressing pulmonary symptoms of dyspnea, cyanosis and unproductive cough, with few physical signs, may be terminated by failure of the right side of the heart. No discrete tumor metastases are seen in the lungs, but microscopically cancer cells are found diffusely infiltrating perivascular, peribronchial, and subpleural lymphatic spaces. In some cases there is an accompanying obliterative endarteritis.²⁰

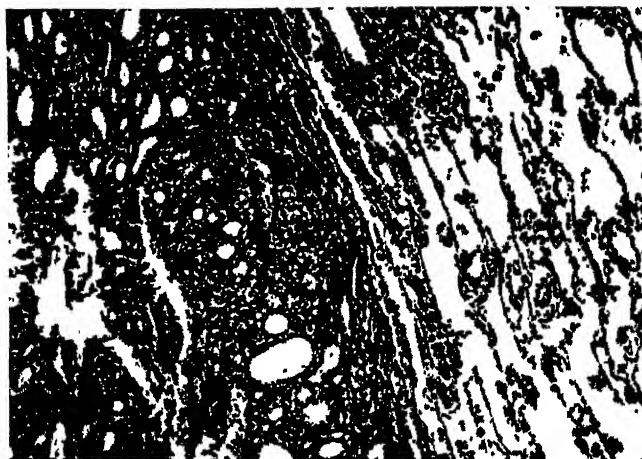


Fig. 163.—Metastatic adenocarcinoma of thyroid in lung.

PNEUMONIA

Inflammation of lung tissue when unaccompanied by necrosis is called pneumonia, though sometimes it is quite logically referred to as pneumonitis. Though commonly of bacterial origin, certain types (e.g., lipoid pneumonia) are due to other irritants. The common types are known as lobar pneumonia, lobular (broncho-) pneumonia, and interstitial pneumonia. Lobar pneumonia is almost always due to pneumococcal infection, whereas bronchopneumonia is caused by a wide variety of organisms. Interstitial pneumonia is a common manifestation of congenital syphilis (pneumonia alba). It also may be of virus etiology or follow certain infectious diseases.

Lobar Pneumonia

Lobar pneumonia is a diffuse pneumococcic consolidation affecting one or more lobes of the lungs. It occurs sporadically, at all ages, and in previously healthy individuals. The disease has a rapid onset with severe prostration, and a serious mortality rate. After a course of one or two



Fig. 164.—Lobar pneumonia. Gray hepatization of lower lobe of lung. The pleural surface has a thick fibrinous exudate. (Courtesy Dr. H. C. Schmeisser.)

weeks, recovery may occur by lysis or crisis, or it may be complicated by organization of the exudate, empyema, abscess formation, pericarditis, endocarditis, or meningitis. In the earliest stage the involved lobe is edematous and

congested, followed rapidly by a stage of red hepatization (consolidation) in which a fibrino-purulent exudate is added to the congestion. This in turn is followed by gray hepatization, in which stage congestion is no longer present, and there is degeneration of cells of the exudate. In favorable cases resolution follows, with increase in the proportion of macrophages, and finally absorption of the exudate and restitution of the lung tissue to its previous healthy condition.

Etiology.—Lobar pneumonia is caused in almost all cases by pneumococci, but it may be caused by Friedlander's pneumobacillus. The pneumococcus is an encapsulated diplococcus which produces green colonies on blood agar, ferments inulin, and is soluble in bile. Pneumococci are not all alike but have different capsular carbohydrates and form specific immunologic types. The particular type may be determined by noting capsular swelling when the organism is in contact with the type-specific serum (Neufeld reaction) or by agglutination reaction of mouse-cultured organisms with specific sera. Pneumococci may be immunologically classified into three main types, and a fourth group which contains numerous specific types of relatively lesser importance. Their approximate incidence in lobar pneumonia, and the approximate mortality (without treatment by specific sera or sulfonamide drugs) is as follows:

	TYPE I	TYPE II	TYPE III	GROUP IV
Incidence, %	30	15	12	43
Mortality, %	35	45	45	20

A considerable proportion of healthy individuals have pneumococci in their sputum, but these organisms are usually of low virulence and belonging to Group IV.

Accessory etiologic factors believed of importance include acute upper respiratory infection, chilling of the body, and alcoholism. Some evidence suggests that bacterial allergy may have an etiologic role.

Pathogenesis.—Pneumococci reach the lungs by way of the respiratory passages. The bacteremia which often is present is believed to be secondary to the pneumonia, rather than primary. Blake and Cecil²² produced experimental lobar pneumonia in monkeys by injection of pneumococci into the trachea. This resulted in an interstitial spread of the infection from the hilum to the periphery of the lung,

with subsequent outpouring of exudate into alveoli. Further clinical and experimental studies have suggested a different course of events in human lobar pneumonia. Robertson and his associates²³ produced in the dog a lobar pneumonia closely resembling that which occurs in humans



Fig. 165.—Lobar pneumonia. An exudate of fibrin and leucocytes fills the alveoli.

by implanting pneumococci suspended in a starch-broth paste into the terminal air sacs. A rapid outpouring of edema fluid quickly dispersed the organisms throughout the lobe by way of air passages and through the pores of Cohn in the alveolar walls, followed later by leucocytic exudation.

Morbid Anatomy.—The pneumonic process goes through a series of stages which are characteristic and roughly indicate the age of the process. There is no sharp dividing line between these stages, which merge into each other; different stages are often evident in different portions of the involved lung. Acute inflammation in the lung has the characteristics of acute inflammation elsewhere, i.e., vascular congestion, and outpouring of a fluid and cellular exudate.

The earliest stage of congestion is characterized by engorgement of blood vessels and outpouring of fluid into alveolar spaces. The involved lobe is heavier and less crepitant than normal, red from the congestion and diapedesis of red cells, and oozes frothy bloody fluid from its cut surface.

The stage of red hepatization rapidly follows; the lobe is consolidated by exudate filling the air sacs and has the consistency of liver tissue. The cut surface is dark red in color and markedly granular. Microscopically, the alveoli are filled by fibrin mixed with red cells and polymorphonuclear leucocytes. These cells are in a good state of preservation, and the vessels in the alveolar walls are congested. Many pneumococci are present in the alveoli. The pleura over the affected lobe is covered by a fibrinous exudate. The bronchi likewise show an acute inflammation.

In the stage of gray hepatization the lobe is still solid and of liver-like consistency, but it is somewhat softer than in the red stage, and less granular. The gray color is due to disappearance of the congestion and of the red cells in the alveoli, and to an increased proportion of leucocytes in the alveolar exudate. The bronchi contain a purulent exudate. Microscopically, the alveolar exudate contains a large proportion of polymorphonuclear leucocytes and relatively less fibrin and red cells. In later periods of this stage the cells of the exudate show degeneration and disintegration. Pneumococci are still numerous in the exudate.

In the stage of resolution the cut surface of the lung has a somewhat translucent jelly-like appearance. At this time many free macrophages are found in the alveoli, arising from transformation of fixed tissue cells. The macrophages engulf and destroy the organisms, which consequently are scarce in this stage. Polymorphonuclear leucocytes are less numerous and are disintegrating.

During recovery the exudate is removed by being coughed up, by phagocytosis and removal by macrophages, and by

liquefaction and absorption. The final result in the uncomplicated case of recovery is restoration of the lung to its previous condition with no residual scars.



Fig. 166.—Organizing pneumonia. The strands of connective tissue can be seen passing from one alveolus to another.

Robertson has pointed out that the mechanism of recovery is a dual one, consisting of a generalized process of immunization which localizes the infection and controls bac-

teremia, and the local macrophage reaction which destroys the pneumococci in the involved lobe. Failure of either process results in death. After recovery, a local immunity to reinfection persists in the involved lobe as long as macrophages are still present.



Fig. 167.—Pneumococcal pericarditis. Note the abundant fibrinous exudate. (Courtesy Dr. H. C. Schmeisser.)

Complications.—While most cases clear up without persisting lesions, a variety of complications may occur. **Empyema** is a persistent purulent pleurisy which follows the pneumonia. When the purulent effusion is large, the lung tissue collapses proportionately. Spread of pneumonia to cause pericarditis occasionally occurs. More rarely, there may be metastatic blood spread to cause pneumococcal meningitis, arthritis, or endocarditis.

In the involved lung tissue several complications may develop. Occasionally there is breakdown of tissue with lo-

calized abscess formation. Secondary infection of the abscess by fusospirochetal or putrefactive organisms results in gangrene. In rare cases resolution of the alveolar exudate fails to occur, and it becomes organized. Such an **organizing pneumonia** is characterized grossly by a dense, solid, fleshy or elastic consistency, to which the term **carnification** of the lung often is applied. Microscopically, there are masses of fibrous tissue which fill the alveoli and join by fine strands passing through small openings in the alveolar walls.

Bronchopneumonia (Lobular Pneumonia)

In bronchopneumonia the inflammatory consolidation is patchy and irregular in distribution. It is usually secondary to or a complication of some other disease or infection, and the etiologic agents include a variety of bacteria and other irritants. The most common microorganisms involved are the pneumococcus (usually from Group IV), streptococcus, influenza bacillus, and staphylococcus. Specific types of bronchopneumonia occur in tuberculosis, tularemia, and plague.

In the pathogenesis of most cases the infection reaches the lung by air passages, with development of a bronchitis and spread to involve alveoli immediately adjacent to a bronchiole. Direct spread then may involve contiguous lobules. In some cases this spread and confluence may be such that a whole lobe is involved, and distinction from lobar pneumonia is not obvious. Pyemia with numerous septic emboli to the lung setting up many small focal areas of inflammation may produce a condition which is grossly very similar to bronchopneumonia.

Examined **grossly**, both lungs usually are found to be involved, but unequally, and the lower lobes in their posterior and basal parts are particularly affected. Firm nodular areas of consolidation are palpable, and pus can be squeezed from the cut bronchioles in these areas. There is usually little or no exudate on the pleural surface, but it is apt to be mottled by alternating bluish and red areas. The cut surface of the lung is moist and red, with some projecting reddish-gray areas of consolidation. These areas can often be felt more easily than seen. Some bluish areas of collapse and lighter areas of emphysema are often present as well. The moist and nongranular character of the cut surface differs from that of lobar pneumonia.

Microscopically, the consolidated areas show alveoli containing mononuclear and polymorphonuclear leucocytes; fibrin and red cells are relatively scarce, though hemorrhagic types may be found, particularly in influenzal and staphylococcal pneumonias. Necrosis of tissue and abscess formation may be present in the cases due to streptococci and staphylococci. The alveolar walls are congested. Bronchioles in the area contain exudate in their lumina and leucocytic infiltration in their walls and extending interstitially for a variable distance around them.

Types of bronchopneumonia having a particular pathogenesis are often given distinctive names, though they have in common many of the features which have been noted. **Hypostatic or terminal pneumonia** is that type often found in patients with heart disease or cerebral hemorrhage. The consolidation is found in lower and posterior parts of the lung where passive congestion has been present. **Aspiration pneumonia** is due to aspiration of material into the lung—e.g., septic material may be inhaled during an operation, particularly if the operation has involved the mouth, pharynx, or upper respiratory tract. **Postoperative pneumonia** may be of the aspiration type, but often it is due to postoperative atelectasis of areas of lung tissue as a result of plugging of bronchi or bronchioles by secretion or exudate. **Suppurative pneumonia**, in which necrosis and pus formation are distinctive features, may be due to staphylococci, hemolytic streptococci or pneumococci.²⁴ **Chemical pneumonias** are those due to irritating or poisonous gases, such as may be used in war.

Interstitial Pneumonia

An interstitial reaction, particularly with mononuclear cells, occurs in the pneumonias which follow and complicate measles, influenza, whooping cough, psittacosis, and other infectious diseases. This type of response has been regarded as the characteristic pneumonic reaction to a virus, or to combined action of a virus and bacteria. Recent epidemics of atypical virus pneumonia^{25, 26} have exhibited interstitial reaction. The change is not an exclusive feature of virus infections, however, as toxoplasmosis may show this change,²⁷ and it may be produced by bacterial toxins or organisms such as the Bordet-Gengou bacillus.²⁸ Virus pneumonias, including the giant-cell pneumonia of infancy, are considered on p. 120.

The gross features of interstitial bronchopneumonia are not characteristic but microscopically there is an interstitial thickening, particularly around the bronchi and bronchioles, and in adjacent alveolar walls. This is due to an increase in the number of mononuclear cells. Bronchioles and alveoli may contain polymorphonuclear leucocytes as well, though even in alveoli mononuclear cells and fibrin may predominate.



Fig. 168.—Acute diffuse interstitial fibrosis of lung. (Section by courtesy of Dr. A. R. Rich.)

Acute Diffuse Interstitial Fibrosis

Hamman and Rich have described an unusual condition of unknown etiology, characterized by a diffuse and progressive fibrosis of alveolar walls. The inflammatory process is marked by edema, hemorrhage, and but few leucocytes, although eosinophiles may be present in the interstitial tissue. There is an absence of stainable bacteria in the lesions. Progressive interstitial fibrosis follows, resulting in deficient aeration of the blood and manifested by dyspnea and cyanosis. Enlargement and failure of the right side of the heart may develop within a few weeks.²⁹

Tularemic Pneumonia

Tularemic pneumonia is found in more than half the fatal cases of tularemia.³⁰ The organisms probably reach the lung by hematogenous spread.

The pulmonary lesion is a nodular or confluent bronchopneumonia, characterized by focal areas of caseous necrosis. In the exudate around such areas mononuclear cells predominate, though some lymphocytes, plasma cells, red cells, and polymorphonuclear leucocytes may be present as well. One sees congestion of alveolar walls and sometimes a swelling of alveolar lining. Pleurisy with effusion and bronchitis frequently accompany the necrotizing pneumonia.

Lipoid Pneumonia

The reactive lesions in the lung due to oily and fatty substances introduced by way of the trachea have been termed lipoid pneumonia. Cod-liver oil and liquid petrolatum are the common causative agents, though olive oil, milk fat, and other substances may produce similar lesions.^{31, 32} The fatty or oily materials gain entrance to the lung by way of the trachea, due to forced feeding, disturbance of the swallowing mechanism, or excessive use of an oily (liquid petrolatum) base in nasal and laryngeal instillations. The condition is most frequent in infants, but an adult type also occurs in which liquid petrolatum is usually the offending agent. The fundamental lesion of lipoid pneumonia is an interstitial proliferative inflammation, which is essentially a foreign body reaction. Macrophages laden with oil or fat, foreign body giant cells and increased connective tissue are the essential features. Adult and infantile types have been described. In "lipoid pneumonia of the infantile type" there is pulmonary consolidation due to fat-laden macrophages and other inflammatory cells in

alveoli and alveolar walls, with but little fibrosis. "Lipoid pneumonia of the adult type" (paraffinoma) is a nodular or tumor-like lesion in which fibrous scarring is prominent. The lesions are commonly located around the hilar region of the posterior and dependent portions of the lung. Liquid petrolatum may be identified in tissue sections by its failure to stain black with osmic acid although stainable by scarlet red. Cod-liver oil in the tissues is characterized by shredding of the oil and acid-fast staining by the Ziehl-Neelsen method.³¹

Rheumatic Pneumonia

While cardiac lesions are of prime importance in rheumatic fever, pulmonary involvement is common. Mitral stenosis gives rise to a chronic passive congestion of the lung, resulting in brown induration. In addition to such changes, more specific primary rheumatic lesions have been described in the lung.³³ This change is an interstitial pneumonitis, focal or widespread, and with a tendency to recurrence. In acute phases congestion and hemorrhage are prominent. Focal areas of inflammation occur, with fibrinoid necrosis, proliferation, and infiltration of large basophilic "Aschoff" cells, and eventual fibrosis. The peculiar focal areas of granulomatous inflammation have been referred to as "Masson bodies."³⁴ The specificity of the lesions is disputed.³⁵ There is a basic similarity to lesions produced by anaphylactic hypersensitivity and in the pneumonitis caused by sulfonamide hypersensitivity.³⁶ In subacute and chronic phases the lung is of rubbery consistency, the toughness being due to interstitial fibrosis and hyperplasia of elastic tissue. Such late changes may be difficult to separate from those due to passive congestion (see below). Pleurisy is also a common manifestation of rheumatic fever.

Hyperplasia of the Pulmonary Alveolar Lining

In a variety of pathologic conditions, alveolar lining cells appear, and probably are derived from "septal cells," normally found scattered in alveolar walls or in the niches between capillaries. Such changes have been described in chronic passive congestion; interstitial and lipoid pneumonias, around tuberculous foci, and in pneumonia alba of congenital syphilis. A few cases of diffuse hyperplasia of alveolar lining cells (pulmonary adenomatosis) have been described, and resemble the pulmonary lesions of jaagsiekte, an endemic infectious disease of sheep.³⁷⁻⁴⁰

CIRCULATORY DISTURBANCES

Congestion

Active congestion in the lung accompanies acute inflammations or follows inhalation of irritants. **Passive** congestion is more common, the hypostatic form being found in almost every autopsy. The lower and posterior parts of the lungs are dark red and firmer than normal. More important is the **chronic passive congestion** which accompanies pulmonary hypertension and failure in the pulmonary circulation. This generalized pulmonary hyperemia may be present for an extensive period and gives rise to brown pigmentation and increased firmness, a condition called "**brown induration of the lung**." The most important cause is mitral stenosis, but aortic stenosis, certain congenital cardiac defects, and other lesions occasionally give the same result. The brown color of the lung is due to hemosiderin pigment, most of which is held in macrophages in alveolar spaces ("heart failure cells"). Parker and Weiss⁴¹ have described the changes in the lung which interfere with function. The thickness of alveolar walls, through which oxygen and carbon dioxide must diffuse, may be increased many times. The alveolar walls have increased collagenous interstitial tissue, thickening of capillary basement membranes, dilated capillaries, and edema. Alveolar lining cells tend toward cuboidal shape. Pulmonary vascular changes are common in such cases and consist of intimal thickening and atherosclerosis of arteries, hyperplastic arteriolar sclerosis, and in some severe cases even arteriolar necrosis. These vascular lesions are promoted by the high intravascular pressure, stagnation of blood, and edema.

Edema

Edema fluid in the lung may be (1) of inflammatory origin, or (2) a transudate occurring in cases of passive congestion or failure of the pulmonary circulation. Inflammatory edema is prominent in early stages of pneumonia, and its high protein content causes it to stain well with eosin. The edematous lung is large, pale, heavy, and pits on pressure. Watery, frothy fluid flows or may be squeezed from the cut surface. In sections the edema fluid appears as a faint eosin-staining material in the alveolar spaces.

Thrombosis, Embolism, and Infarction

Blockage of pulmonary arteries by embolism is common, but primary thrombosis is relatively rare. Thrombi which give rise to pulmonary embolism most commonly originate in the iliac veins, femoral veins, pelvic veins, prostatic venous plexus, vena cava, and right auricle. Postoperative pulmonary embolism is most apt to follow abdominal or pelvic surgical procedures. If the embolus blocks the pulmonary artery or one of its large branches, it may cause rapid death. The actual mechanism of death appears to be a sympathetic-inhibitory reflex or shock.⁴² There is insufficient time for development of an infarct of the lung in such rapidly fatal cases. Demonstration of the embolus at autopsy often can be facilitated by opening the pulmonary artery in situ before removal of the heart.

Blockage of smaller pulmonary arteries by emboli results in infarction of lung tissue if there is already some interference with the pulmonary circulation, such as passive congestion. Pulmonary infarcts are practically always red and hemorrhagic. They form bulging, dark red, firm, conical areas, with their base at the pleural surface. Microscopically, the whole area of infarction, including alveolar spaces, walls, and capillaries, is stuffed with blood. In later stages necrosis of alveolar walls may be observed, and there is decolorization of the blood.

Belt⁴³ has listed criteria for distinguishing pulmonary emboli and thrombi. An embolus tends to be coiled, twisted, impacted, or riding a bifurcation; its shape may not conform to that of the vessel in which it lies; it may have freshly broken ends; it is usually a red clot composed chiefly of fibrin and red cells since it arises in a slow-moving venous stream. A thrombus is usually white or light pink, being composed chiefly of platelets and leucocytes, since it is laid down in a faster moving stream; it is usually attached to the vessel wall, has a sessile base, and is molded to the shape of the vessel.

Blast Injury

Pulmonary hemorrhage associated with thoracic trauma or asphyxia is common in both peace and war injuries. In war experience, "blast injury" or pulmonary concussion due to a nearby bomb or other high explosive, may produce fatal pulmonary hemorrhage without external evidence of trauma.⁴⁴ The lungs show bilateral and roughly symmetrical

hemorrhagic consolidation deep in their substance. There is an associated general pulmonary congestion, and the hemorrhage may be progressive. Microscopically, the appearance is similar to that of a recent infarct, but some areas may show fibrin and monocytes as well as red cells in alveolar spaces, and so simulate in appearance the red hepatization stage of pneumonia.⁴⁵ Ross⁴⁶ has pointed out that in compression asphyxia the lesion differs in that the hemorrhages are mainly subpleural and in the lines of the ribs, with emphysema outlining rib markings. In pulmonary hemorrhage due to traumatic impact of a solid, the hemorrhage may be unilateral, related to site of the blow, and around this point the lung is torn or contused.

Arteriosclerosis

Pulmonary arteriosclerosis of mild degree is common but rarely of clinical importance. In larger arteries it is evident grossly as intimal atherosclerosis. Hypertension and congestion in the pulmonary circulation (e.g., in mitral stenosis) lead to vascular changes.

There is also a rare condition of primary sclerosis of pulmonary arteries, associated with hypertrophy of the right side of the heart, and usually resulting in death from heart failure.⁴⁷ Some of these cases, particularly when associated with marked cyanosis, are designated *Ayerza's disease*. However, the concept of *Ayerza's disease* has been variable, and in many cases it has been considered of syphilitic origin.

ATELECTASIS

Atelectasis is an incomplete dilatation or a collapse of lung tissue. The three main causes are (1) failure of expansion in the newborn (congenital), (2) compression of lung tissue, and (3) bronchial obstruction. Atelectasis does not interfere with respiratory function unless areas of considerable size are involved.

In many stillborn children the lungs are completely atelectatic and airless. Infants who live for a few days have lungs with patchy areas of atelectasis or incomplete expansion. Compression atelectasis results from pressure against lung tissue, as by air, transudate, or exudate in pleural cavity, or by tumors. Bronchial obstruction results in atelectasis due to absorption from the nonaerated portion of lung.

Atelectatic lung tissue is dark red or blue in color due to congestion, firm, noncrepitant, and depressed below sur-

rounding surfaces. Microscopically, the alveolar walls are pressed together forming more or less parallel bands separated by narrow elongated alveolar spaces. If atelectasis is present for a considerable period, fibrosis may occur and re-expansion become impossible.

Acute massive collapse refers to the rapid atelectasis of the whole or a large part of a lung. The mediastinum is displaced toward the affected side, and there is evidence of respiratory difficulty. It is an occasional complication of abdominal operations, peritonitis, diaphragmatic pleurisy, and paralyzes of diphtheria. Bronchial obstruction and interference with the cough reflex are believed to be the important factors in causation.⁴³

PULMONARY EMPHYSEMA

Emphysema is the condition of abnormal increase of air content of tissues. In the emphysematous lung there is distention of alveoli, with loss of elasticity, and thinning or rupture of alveolar walls. **Acute pulmonary emphysema** may be observed in death from asphyxia, anaphylactic shock, and certain poisonous gases. **Chronic emphysema** occurs in a large lung (hypertrophic or obstructive) type and a small lung (senile) type.⁴⁹

In **obstructive emphysema** the lungs are voluminous, pale, dry, and of peculiar pillow-like consistency due to loss of normal elasticity. The lungs fail to collapse when the chest is opened. Large blebs or bullae often occur at the apices and along the margins. Microscopically, the alveolar spaces are enlarged, the walls appearing stretched, thin, bloodless, and often ruptured. The constriction of vessels in the alveolar wall causes the pallor and dryness of the lung tissue.

Emphysema is associated with an increase in the residual air content of the lungs, and a proportionate decrease in vital capacity. The chest tends to be barrel-shaped, with a wide costal angle, and a low position of the diaphragm. The decreased pulmonary mobility and elasticity, and obliteration of alveolar capillaries, tend to cause stagnation in the pulmonary circulation and throw more work on the right heart. There follows an hypertrophy of the right heart (cor pulmonale), and eventually there may be failure and passive congestion. The etiology of this type of emphysema is often obscure, but partial bronchial obstruction appears to be the most important factor.

Senile emphysema, also associated with a barrel-shaped chest and hyperresonant lungs, is usually seen during or after middle age. The primary change appears to be a stiffening and straightening of the thoracic spine, which is associated with degenerative changes in intervertebral discs. The lungs follow the change in shape of the chest but are not actually enlarged. They collapse on opening the chest, since their elasticity is not greatly impaired. Respiratory function is but little impaired except in those cases in which the lung has been overstretched.



Fig. 169.—Emphysematous areas in lung. (Courtesy Dr. H. C. Schmeisser.)

Pulmonary interstitial emphysema is a condition in which air is present in interstitial tissues of the lung rather than in alveolar spaces. Air escapes through ruptured alveolar bases into sheaths of pulmonary vessels, precipitated by a pressure gradient of air in alveoli to perivascular sheaths in cases

where alveoli are overexpanded or blood vessels are not filled to the normal extent. Predisposing conditions are (1) general overinflation of lung tissue, (2) atelectasis of an area of lung with overinflation of adjacent areas, and (3) decreased blood supply to pulmonary vessels with hyperinflation or increased intra-alveolar pressure. The air may travel along vascular sheaths to the mediastinum (pneumomediastinum), work upward to the neck, face, and axillae (subcutaneous emphysema) and downward along the aorta and esophagus into the retroperitoneum. Cyanosis may result from venous stasis due to collapse of pulmonary vessels and dyspnea from interference with respiratory movement. Cardiac disturbance may result from pressure of the distended lungs or pneumomediastinum, or from lack of blood due to the venous congestion. Continued accumulation of air in the mediastinum, unless withdrawn, may be fatal from interference with respiration and circulation.^{50, 51}

PNEUMOCONIOSES

Pneumoconiosis refers to the pulmonary changes due to the inhalation of dust. These changes depend on the type and amount of dust inhaled, length of time of exposure, and the presence of associated infection, particularly tuberculosis. There are four important types.^{52, 53} (1) Anthracosis, due to inhalation of carbon pigment, is almost universal in occurrence but is not associated with functional changes and hence is unimportant clinically. (2) Silicosis, due to inhalation of free silica, is an important occupational disease among miners and others working in rock. Because of its specific chemical nature it produces a reaction in the lung characterized by the development of nodular areas of hyaline fibrosis. It is often associated with tuberculosis and accelerates this infection. The pulmonary fibrosis predisposes to right heart failure. (3) Asbestosis, due to inhalation of asbestos fibers, is relatively uncommon. It produces a diffuse fibrosis of the lung. Characteristic "asbestos bodies," which are elongated, club-shaped fibers coated with iron pigment, are found in the lung tissue and may appear in the sputum. It causes no particular predisposition to tuberculosis. Right heart failure may result from the pulmonary fibrosis. (4) Silico-siderosis occurs among hematite miners and is characterized by lungs of a bright brick-red color.

Anthracosis.—A deposit of inhaled carbon pigment is found in some degree in all adult urban dwellers. While the

normal color of the lung, as seen in an infant, is grayish pink, the adult lung is flecked by focal and linear deposits of black pigment, evident on both the pleural and cut surfaces. Through function of alveolar phagocytes and lymphatics the pigment becomes concentrated in the lymphoid tissue of the lungs, peribronchial nodes and mediastinum. The pigment tends to accumulate particularly in areas where inflammation or fibrosis has blocked lymphatics. The pigment itself does not stimulate fibrosis. Air spaces are visible in the pigmented areas, and respiratory function is undisturbed.

Silicosis.—Silicosis is the most important of the pneumoconioses because of its frequency as an occupational disease, the severity of the fibrosis, and its promotion of serious tuberculous infection. Inhaled particles of silica become concentrated in the pulmonary lymphatic system, and here they stimulate connective tissue proliferation. Nodules of hyalinized, collagenous, concentric laminae are formed. Carbon pigment is usually trapped in the same area, so that some black pigment is evident in the nodule. The particles of silica may be identified by a polarizing microscope.

In early stages the silicotic nodules are too small to be identified grossly, but ultimately they develop into nodules, 3 or more millimeters in diameter, and with sharply defined borders. Islets of this collagenous tissue are scattered through the lung, under the pleural surfaces, and in tracheobronchial lymph nodes. Eventually, massive conglomerate areas of fibrosis may result. Most of the fatal cases terminate with tuberculous infection. Other complications which may develop are cardiac hypertrophy and dilatation, particularly of the right side of the heart, emphysema, and carcinoma of the lung. The degree of importance of silicosis in the etiology of pulmonary carcinoma is still undetermined.⁵⁴

Asbestosis.—Asbestos is a mineral fibrous structure, composed essentially of magnesium silicate. Inhalation of the fibers occurs mainly in the factories during the carding process in which the fiber is separated from the crushed mineral. Inhalation over a period of seven or more years is usually required to produce the disease. The fibers are deposited in the bronchioles and stimulate fibrosis mechanically rather than by specific chemical action. The lower lobes particularly are affected, and the result is a

diffuse rather than nodular type of interstitial fibrosis. Emphysema, bronchiectasis, and interference with respiratory function may result. Termination is usually by infection or cardiac failure. Tuberculosis occasionally supervenes, but asbestosis does not particularly predispose to tuberculosis.

Grossly, the involved lung shows irregular patches and strands of grayish dense irregular scar tissue. Dilated emphysematous air spaces are evident in the involved tissue.



Fig. 170.—Asbestosis of lung. Note the bulbous ends and the haustriation of the asbestos bodies, and the giant cells.

The characteristic asbestos bodies occur singly or in clumps as elongated fibers, of variable size and form (up to 140 microns in length). One or both extremities of the fiber are bulbous; the body is slender and haustriated or segmented. The color is yellowish, greenish yellow or brown, due to iron pigment deposited on the surface, and they stain well with the Prussian blue method for iron.⁵⁵

Silico-Siderosis.—Silico-siderosis is due to inhalation of iron-containing hematite by hematite miners. The lungs

have a striking brick-red color. Some silica is usually inhaled as well. A diffuse or nodular pulmonary fibrosis may be produced.

Siderosis of Welders.—Electric arc welders inhaling concentrated fumes in unventilated spaces may develop a siderosis which results in nodular shadows on a chest roentgenogram. The iron pigment is held in perivascular lymphatic tissue, and is distinguishable from the similar-appearing anthracotic pigment by the Prussian blue reaction. No fibrosis develops to cause functional impairment of the lungs, and there is no predisposition to tuberculosis or other lung infections.⁵⁷

PLEURA

Diseases of the pleura are mainly effusions, inflammations, and tumors. With effusions into the pleural cavity, corresponding collapse of lung tissue occurs. The collapse may be limited to one side by immobility of the mediastinum, or locally limited by adhesions.

Hydrothorax.—Hydrothorax is the accumulation of edema fluid or transudate in the pleural cavity. It occurs in conditions of generalized edema, as in renal or cardiac disease, or rarely may be caused by local conditions such as tumor or aneurysm. The fluid is clear, light yellow, of low specific gravity (below 1.015), and it has a low protein content. In some cases the fluid is milky due to fat content (chylous hydrothorax).

Hemothorax.—Blood in the pleural cavity may occur in cases of thoracic trauma, or from rupture of an aneurysm. A bloodstained pleural fluid is more common than true hemothorax. Its occurrence is usually associated with tuberculosis, or malignant tumor of the lung or pleura.

Pneumothorax.—Air in the pleural cavity may be introduced from without by wounds or therapeutic procedures, or result from a rupture of lung into pleural cavity. The commonest causes of the latter are tuberculosis and rupture of an emphysematous bleb. In many cases air in pleural cavity is associated with a serous or inflammatory exudate.

Pleurisy.—Inflammation of the pleura is usually a spread from the lung. Less commonly it is due to spread from abdomen or mediastinum, or is blood-borne and appears to be primary in the pleura. Most cases are due to infection with tubercle bacilli, pneumococci, or streptococci. The apparently primary forms usually are due to tuberculosis or

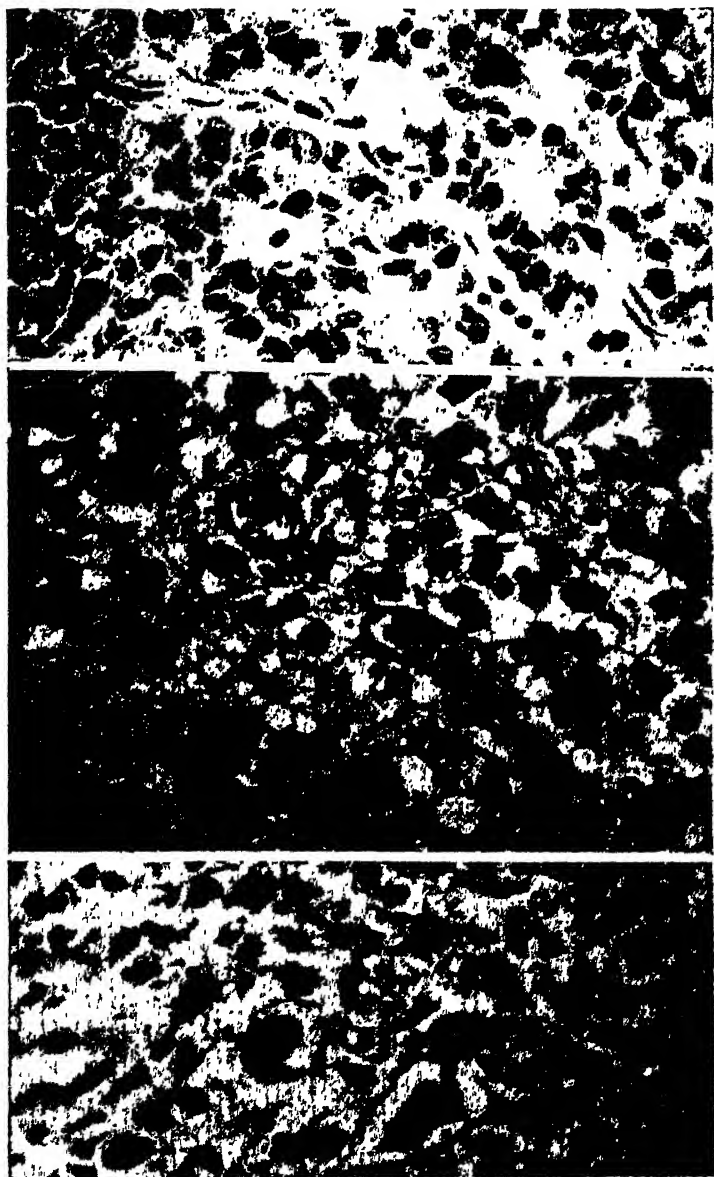


Fig. 171.—Mesothelioma of pleura.

rheumatic fever. Pleurisy is classified according to the type of exudate as fibrinous (dry pleurisy), serofibrinous (pleurisy with effusion), and purulent (empyema). The fluid in pleurisy is cloudy or contains flakes of fibrin, has a relatively high specific gravity and high protein content. The exudate containing fibrin and inflammatory cells is evident in sections through the inflamed pleura. Pleurisy may resolve and leave little trace, but often organization results in a thickened scarred area of pleura or fibrous adhesions between visceral and parietal layers.

Empyema most commonly is the result of pneumococcic or streptococcic infection of the lung. Organization and formation of adhesions tend to localize the pus in various parts of the pleural cavity. A thick organizing wall of exudate may line the cavity, covering both visceral and parietal surfaces.

Pleural Tumors.—Most tumors involving pleura are extensions from malignant tumors in the lung, but rare primary pleural tumors occur. The primary benign tumors arise from subpleural tissues and include fibromas, lipomas, chondromas, and angiomas.

Mesothelioma is a rare primary malignant tumor arising from pleural lining cells. It may form flattened nodular tumor masses on both visceral and parietal layers, or spread diffusely over pleura forming a thick layer of tumor tissue. Microscopic characteristics of both epithelial and connective tissue tumors may be present, with a sarcomatous appearance in some areas, but also tending to form gland-like spaces or channels. Spread may be by invasion of lymphatics and metastasis to mediastinal lymph nodes. Abundant hemorrhagic pleural fluid is a usual accompaniment.

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CHAPTER XV

LIVER, GALL BLADDER, AND PANCREAS

THE LIVER

Structure and Function

The liver has a double blood supply, portal and hepatic, but the circulation to the right and left sides of the liver is fairly distinct. This circulatory division of the liver does not correspond with the anatomic lobes, but the right and left halves are divided by a line passing through the middle of the gall bladder fossa to the junction of the hepatic veins with the inferior vena cava. The portal stream from the spleen and stomach goes mainly to the left side of the liver, and from intestines mainly to the right side.

Microscopically, the liver appears divided into lobules, at the center of each being a central (efferent) vein, and arranged around the periphery are portal areas, each containing a bile duct, hepatic artery, and portal vein. The cords of liver cells enclose bile canaliculi and blood sinusoids. In the wall of the latter are Kupffer cells, which are highly phagocytic and form a part of the reticulo-endothelial system.

The liver is the largest organ in the body and its functions are many and varied. It is concerned with the excretion of bile, but bile pigment is formed only partly in the liver, other components of the reticulo-endothelial system (spleen, bone marrow) playing a major role. The liver forms bile salts and is important in various other biochemical processes, such as formation of plasma proteins, heparin, prothrombin and fibrinogen, fat metabolism and storage, urea and amino-acid formation, glycogen storage, etc. In the fetus the liver is a blood-forming organ.^{1, 2, 3}

An important feature of the liver is a marked capacity for regeneration following injury or destruction of its cells, a feature which is important in compensation for effects of injury to liver cells. There is nodular overgrowth of localized regenerating areas (multiple nodular hyperplasia) in which mitoses often can be found, and new bile duct formation is prominent. The compensatory hyperplasia is

prevented by deficiency or obstruction in the portal circulation (e.g., in portal cirrhosis) and by confinement and compression due to fibrosis.

Congenital abnormalities are not common or important in the liver. **Riedel's lobe** is a downward projection of the right lobe. Acquired changes in form include transverse grooves due to tight clothing. Anteroposterior depressions on the upper surface of the liver are due to pressure of muscle bundles of the diaphragm.

Autolysis

Postmortem autolytic changes develop quite rapidly in liver tissue. Bluish-black discoloration may occur in the portion of liver adjacent to the transverse colon. Foamy liver results from post-mortem infection of the liver by gas-forming organisms (e.g., *C. welchii*) from the intestinal tract, the bubbles of gas so produced honeycombing the liver tissue.

Degenerations

Cloudy swelling is common in the liver as a result of acute infections. The liver is enlarged, has a tense capsule, softer consistency, and a paler, more opaque appearance than normal. Microscopically the liver cells are swollen, have distinct margins and pale granular cytoplasm.

Amyloid infiltration is common in the liver as well as in the spleen and kidney in cases of tuberculosis and chronic suppuration. The amyloid appears as a hyaline material between the lining cells of the sinusoids and the liver cells. Its continued accumulation causes compression, atrophy, and disappearance of the liver cords.

Hyaline masses may be found in the cytoplasm of liver cells in portal cirrhosis, apparently representing an early and specific type of degenerative change in the liver cells.

Glycogen is normally abundantly present in the cytoplasm of liver cells but is much depleted by the wasting which precedes death from many diseases. Cytoplasmic glycogen is also reduced in diabetes mellitus, although the amount in the liver cell nuclei may be increased and give the nuclei a clear, glassy appearance. Cytoplasmic glycogen is abnormally increased in **von Gierke's glycogen storage disease**. This is a congenital defect of glycogen mobilization, seen as a rare condition in infants and children. Enlargement due to the accumulation of glycogen may involve the heart or spleen as well as the liver.

Fatty change in the liver is a common event and may be of very severe degree. Fatty degeneration occurs with a variety of infections and intoxications. Prolonged passive congestion tends to cause fatty degeneration in central parts of the lobules. Distinctions between fatty degeneration and



Fig. 172.—Extreme fatty change of liver.

fatty infiltration are unreliable, and in most cases the infiltration of fat into the liver is a pathologic process. Fatty livers are found in association with obesity, chronic alcoholism, malnutrition and wasting diseases (e.g., tuberculosis and malignant tumors), some cases of diabetes mellitus, and as a result of certain poisons such as phloridzin, carbon tetrachloride,

chloroform, and ether.⁴ In some cases of sudden death in young adults, marked fatty change in the liver has been the only finding.⁵ The increase is in neutral fat, the mechanism apparently being some interference with normal



Fig. 173.—Chronic passive congestion of liver. Fatty degeneration and atrophy around the central vein area in the upper half of the figure.

carbohydrate-fat catabolism, often by interference with the proper oxidation of fat. Alcohol appears to produce its effect by interference with tissue oxidation. In experimental

animals, deficiency of choline (dietary) or of lipocaic (depancreatized dogs) produces marked fatty changes in the liver. The role of such deficiencies in human pathology is not yet established.

The fatty liver, such as seen in chronic alcoholism, is enlarged, has rounded borders, a tense capsule, a yellow or a yellowish-red color, fairly firm consistency, and some greasiness of the cut surface. Microscopically the fat is most prominent around the central part of the lobules, but when the fatty change is marked, the distribution is diffuse and the fat is in the form of large globules.

Circulatory Disturbances

Chronic passive congestion is a common and prominent finding in the liver, an organ highly susceptible to circulatory deficiency. Cardiac insufficiency, e.g., due to rheumatic endocarditis, leaves its mark on the liver early and prominently. The effect is particularly in the central parts of the lobules, where stagnation and accumulation of blood dilate the central vein and adjacent portions of the sinusoids. The liver cells, first around the central veins, but gradually extending out to the periphery, undergo atrophy due to anoxemia and compression. Degenerative changes, particularly of a fatty type, tend to occur. In some severe cases there may be actual necrosis. Grossly, the contrasted pattern of red areas (due to blood-stuffed vessels) and yellowish-brown areas (liver cells with fatty degeneration) produces a characteristic "nutmeg" appearance. Long-standing congestion results in the so-called "cardiac cirrhosis" (see p. 390).

Hemorrhage in the liver, which occurs in eclampsia and other conditions, is distinguished from congestion by finding red cells outside the sinuses, e.g., between the sinusoidal endothelium and the liver cells. **Edema** in the liver is distinguishable by the presence of a fine web of granular precipitated protein material between the sinus endothelial lining and the liver cell cords.

Infarction is rare in the liver, presumably because of the abundant and double blood supply. When it occurs, it is most often due to blockage of intrahepatic branches of the portal vein, although some infarcts have developed after ligation of the hepatic artery.

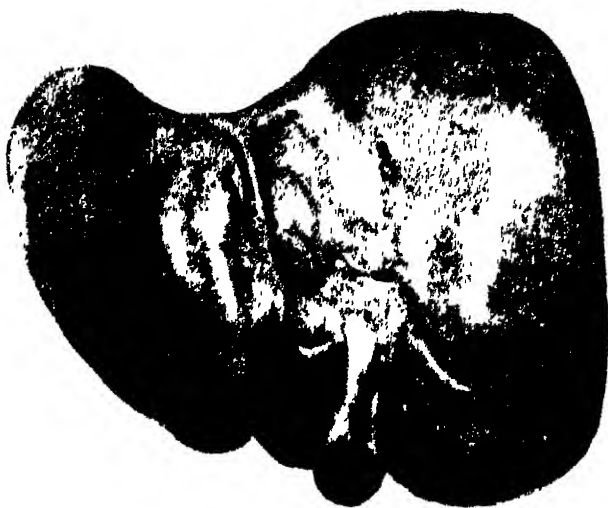
Necrosis

Liver cells undergo necrosis as a result of a variety of poisons of chemical, infectious, and metabolic origin. Adequate stores of glycogen in the liver cells appear to give some protection. The lesions may be classified roughly according to their distribution into the following types: (1) diffuse necrosis, e.g., acute yellow atrophy; (2) focal necrosis, i.e., small necrotic foci distributed without any constant relationship to particular areas of the liver lobules; and (3) zonal necrosis, in which the areas of necrosis are in fairly constant relationship to a particular part of the liver lobules. The zonal necroses may be: (a) central, i.e., in the central vein region; (b) mid-zonal, and (c) peripheral, or in portal areas.

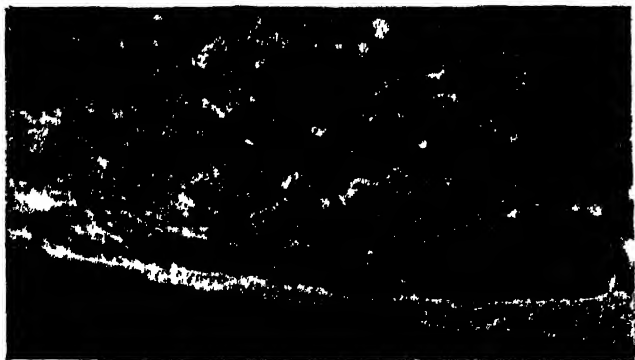
Acute Yellow Atrophy.—Acute yellow atrophy is an uncommon condition in which there is diffuse necrosis, with loss of liver cells, so that the liver is small (atrophic), soft, wrinkled, and mottled with yellow and red areas. It occurs in young adults, occasionally in children, and in some instances in pregnancy either with or without associated eclampsia. The classical cases are of unknown etiology, but in some instances diffuse hepatic necrosis is associated with chemical poisoning, e.g., by arsenicals or chloroform. The acute form is fatal after a short duration with fever, gastrointestinal upset, disturbances of hepatic and renal functions, jaundice, crystals of leucine and tyrosine in the urine, and coma.

Except in the most acute cases the liver is shrunken, often to half its normal size. The capsule is wrinkled, soft, opaque and of mottled, patchy yellowish and red color. In early stages the yellowish color predominates, but later, when the liver cells have extensively disintegrated, a red color is prominent. Microscopically one sees loss of nuclei, granular and fatty degeneration of cytoplasm, and breaking up, disorganization, or complete disappearance of many cells.

Subacute Yellow Atrophy.—Subacute yellow atrophy refers to those milder cases in which there is recovery, or in which progress of the disease is slower, so that death occurs at a later stage or only after repeated attacks. Here there is opportunity for removal of the necrotic cells, regenerative hyperplasia from remaining liver tissue, and development of fibrous tissue. Nodules of hyperplastic liver cells are separated by connective tissue, and bile duct proliferation is in evidence. Complete healing may be achieved, but in some cases the changes are progressive and end in hepatic insufficiency, or liver cell carcinoma may develop in the hyper-



1



2.

PLATE IX.—Liver in eclamptic toxemia of pregnancy. 1. Posterior surface, and 2. cut surface, showing irregular areas of hemorrhage. (From Dieckmann, W. J.: *The Toxemias of Pregnancy*, St. Louis, The C. V. Mosby Company, 1941.)

plastic nodules. The healing or healed stage is often referred to as multiple nodular hyperplasia or toxic cirrhosis.

Focal and Zonal Necroses.—**Focal necroses**, which have no special or constant site in the liver lobules, occur in a variety of severe infections, such as typhoid fever, pneumonia, diphtheria, tularemia (Fig. 174), etc.

Central necrosis is the commonest type of zonal necrosis. It occurs with severe chronic passive congestion, particularly if there is added infection with streptococci. A variety of poisons, some of industrial importance, such as trinitrotoluene, carbon tetrachloride, and chloroform, produce central necrosis.

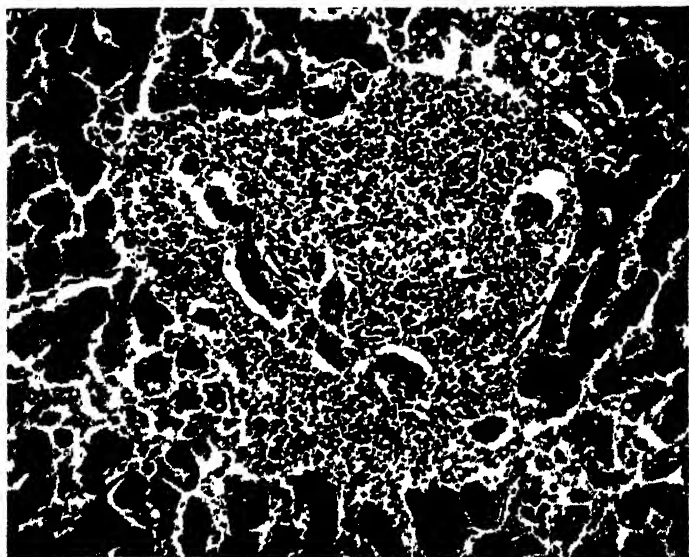


Fig. 174.—Liver, focal necrosis in tularemia.

Mid-zonal necrosis occurs in certain infective conditions and is particularly a characteristic of yellow fever. In this latter condition there are rounded hyaline cytoplasmic masses (Councilman bodies) in cells of the mid-zonal region, and also nuclear inclusion bodies. Belt⁶ has pointed out that similar hepatic lesions may be found in cases of fatal burns.

Peripheral necrosis is often seen in phosphorus poisoning and in eclampsia, though in the latter condition the necroses are by no means constant in their position but are often focal in distribution and hemorrhagic in character.

Eclampsia.—Eclampsia is a toxic complication of the later months of pregnancy (see pp. 312 and 604), in which hypertension, albuminuria, edema, and convulsions are prominent features. The lesions in the liver are the most striking, but they cannot be correlated with the severity of the disease and are probably of less importance than the renal changes. Areas of confluent necrosis and associated hemorrhage may be patchily scattered through the liver substance, and irregular areas of hemorrhage beneath the capsule give the liver a grossly mottled appearance.

Hepatorenal Syndrome

Renal changes resulting from hepatic damage are a common observation, the association being loosely referred to as the "hepatorenal syndrome." The mechanisms of this association are but poorly understood, and several unrelated conditions probably are lumped together under this terminology. Excess of bile pigment (jaundice) is known to be damaging to renal tubular epithelium. It produces mild degenerative changes (cholemic nephrosis—see p. 301).

Epidemic Hepatitis

Epidemic hepatitis is a transient, and usually mild, icteric condition which occurs in epidemic form, and also sporadically. The mortality is usually less than 0.4 per cent. The sporadic cases often have been referred to as catarrhal jaundice, with the supposition that an inflammatory swelling of the common bile duct caused obstruction. However, there is an actual hepatitis and hepatic necrosis, and in fatal cases the liver lesions are those of acute yellow atrophy. The jaundice appears to be due to obstruction of the intralobular bile canaliculi. Associated lesions in fatal cases include cholemic nephrosis, regional lymph node and splenic enlargement due to cellular proliferation and congestion, and hemorrhagic phenomena in various tissues due to disturbances of prothrombin and vitamin K as a result of destruction of liver. In some cases ascites, phlegmonous inflammation of the intestinal tract, and degenerative cerebral lesions may be found. In nonfatal cases there is usually complete restoration of the hepatic tissue without significant scarring. This is due to the marked regenerative ability of the hepatic cells when the injury is not continued and the hepatic framework and vessels are not destroyed.⁷



0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Fig. 175.—Epidemic hepatitis, nineteenth day. Regenerating tissue is evident on the right. (From Lucké, Balduin. *Am. J. Path.* 20: 1944.)

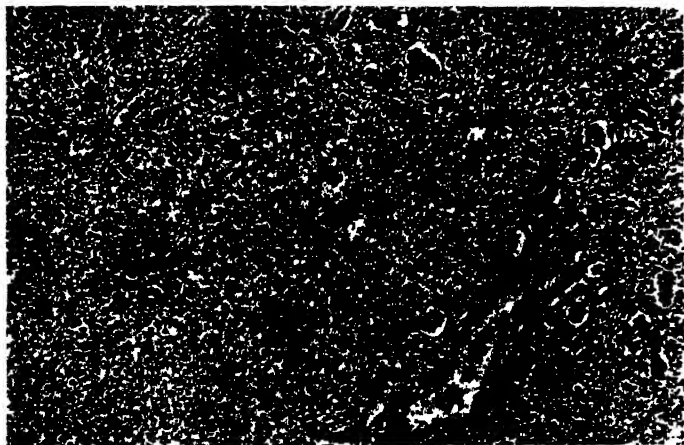


Fig. 176.—Epidemic hepatitis. Microscopic appearance of liver, shown in Fig. 175. (Courtesy Lt. Col. Balduin Lucké.)

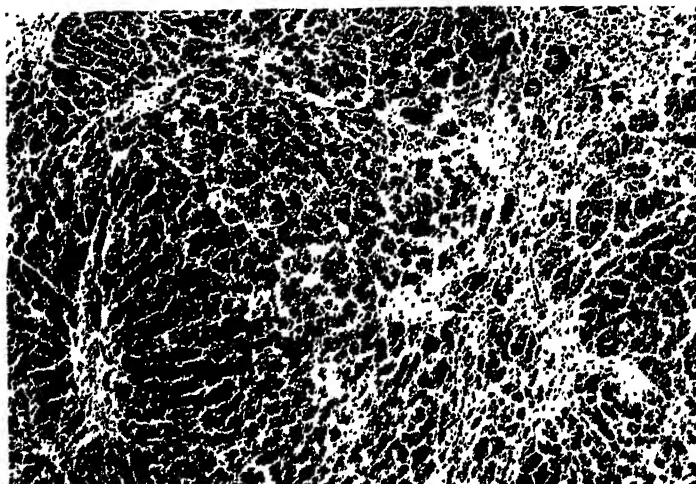


Fig. 177.—Epidemic hepatitis ninety-third day, showing regenerating nodule of liver parenchyma. (From Lucké, Balduin: *Am. J. Path.* 20: 595, 1944.)

Cirrhosis of the Liver

Cirrhosis refers to a fibrosis or scarring of the liver, which is progressive and not simply the stationary healed end stage of an injury. There are several varieties which differ in etiology, nature, form, and effects: (1) Portal cirrhosis; (2) biliary cirrhosis, in which bile duct obstruction is the important factor; (3) pigment cirrhosis, the liver change in hemochromatosis; (4) syphilitic cirrhosis; (5) cardiac or central cirrhosis, the result of a passive congestion of long standing; and (6) parasitic cirrhosis, due to schistosomiasis or clonorchiasis.

Portal Cirrhosis.—Portal cirrhosis (Laënnec's cirrhosis, alcoholic cirrhosis, hobnail liver) occurs at any age but most commonly in middle life, and it is more frequent in males. A history of chronic alcoholism is present in 50 per cent or more of cases,⁸ but it also develops in total abstainers. Bouts of jaundice or other evidences of hepatitis occur in some cases, but functional liver failure is usually not a prominent feature. Ascites is the most constant and striking result. There is obstruction of the portal circulation and collateral channels of venous return develop. Death may be sudden from the rupture of varices of the esophagus.

GROSS APPEARANCE.—The liver tends to be enlarged in early stages, but when seen is usually atrophic and smaller than normal. The general shape is normal, and the color reddish brown, or yellowish if there is associated fatty change. The whole outer surface is nodular, due to rounded projecting masses of liver cells, 2 to 5 mm. in diameter, separated by retracted grayish connective tissue. Consistency of the tissue is much increased. On the cut surface, an interlacing network of gray translucent connective tissue separates prominent remaining lobules of liver cells.



Fig. 178.—Portal cirrhosis of liver. (Courtesy Dr. H. C. Schmeisser.)

MICROSCOPIC APPEARANCE.—Microscopically, the normal architecture of the liver is completely upset by bands of connective tissue, which redivide the liver into irregular nodules having no constant relationship to central veins or portal regions. Most of the connective tissue is fairly young, only slightly hyalinized, and infiltrated by mononuclear chronic inflammatory cells, mainly lymphocytes and plasma cells. Small bile ducts are numerous and prominent in the connective tissue areas. In early stages of the process degenerative

changes are evident in the liver cells and, most characteristically, there is a hyaline accumulation in their cytoplasm, as described by Mallory. In some cases fatty change is a prominent feature associated with the cirrhosis.

ETIOLOGY.—The etiology is still unsettled and much debated. Cirrhosis has been produced experimentally in animals by repeated doses of certain poisons, such as carbon tetrachloride, tars, and combinations of phosphorus and alcohol, manganese chloride and phenylhydrazine, and chloroform with infection. Mallory also found that lead would induce cirrhosis. Alcohol alone has quite regularly failed to produce cirrhosis in experimental animals, though when combined with a high fat diet in a prolonged experiment, it has done so.¹² Dietary deficiency also has resulted in cirrhosis.^{10, 11} Nutritional cirrhosis in experimental animals has been produced in rats by a diet low in casein, but preventable when methionine, or cystine plus choline is added to the diet. The cirrhosis is similar to portal cirrhosis of man except for the presence of a golden-brown fluorescent pigment, ceroid. Ceroid is believed to be of lipoidal nature, and developed from liver cells containing fat during the development of cirrhosis.¹⁴

Clinical experience indicates that alcoholism is a factor in many cases of cirrhosis, although the relationship is not necessarily a direct one.¹³ Contaminants of alcoholic beverages, such as minute amounts of lead or copper, were suggested by Mallory to be the additional necessary factor. Connor¹² has indicated that it is dietary insufficiency in combination with alcoholism that results in the liver damage and has argued for a direct metabolic effect of alcohol, suggesting that it interferes with tissue oxidation mechanisms. According to his findings, the fatty liver so characteristic of chronic alcoholism proceeds gradually, if the individual survives and the insults to the liver continue, to the development of portal cirrhosis.

No doubt other types of recurrent or continuing hepatic injury can proceed to cirrhosis as the terminal stage. In some cases the acute exacerbations of hepatitis are clinically evident. The possible role of methionine or cystine and choline deficiency in the production of cirrhosis in man has not yet been made clear by sufficient investigation.¹⁵

EFFECTS.—The effects of portal cirrhosis in disturbing the portal circulation are usually more prominent than failure of liver function. Ascites is the outstanding feature and mainly is the result of congestion and increased pressure in the portal veins, but reduction of plasma proteins is an important factor contributing to the accumulation of fluid.

Perfusion experiments have indicated that in some cases portal hypertension may be contributed to by an increased hepatic arterial inflow transmitted to the portal side by abnormal arteriportal anastomoses.¹⁵

The gradually developing obstruction in the portal circulation permits the development of a collateral venous circulation. The cutaneous vessels over the abdomen and back become distended and prominent. Varices of esophageal veins commonly develop, the anastomoses with these from the portal



Fig. 179.—Varicose veins at lower end of esophagus. From a case of portal cirrhosis of the liver. (Courtesy Dr. H. C. Schmeisser.)

circulation being composed of vessels from the coronary veins and from the left gastroepiploic veins and vasa brevia. In the lower third of the esophagus the rich anastomoses of submucosal veins are poorly supported by connective tissue. Hence this is a frequent site for varices and venous rupture. Varices of hemorrhoidal veins are much less common in association with cirrhosis.

Testicular atrophy is a common accompaniment of cirrhosis, particularly in patients under 50 years of age. The extensively damaged liver apparently fails to inactivate

estrogens, to excess of which the testis is susceptible.¹⁶ A similar explanation is possible for the occasional occurrence of gynecomastia and arterial spider nevi of the skin.

The spleen is enlarged and congested in cases of portal cirrhosis as a result of the obstruction to the portal circulation. **Banti's syndrome** (see p. 416) frequently includes portal cirrhosis. In **Wilson's disease** (hepatolenticular degeneration) cirrhosis is associated with degenerative changes in basal ganglia of the brain.

Biliary Cirrhosis.—Much less common than the portal type, biliary cirrhosis is due to obstruction in some part of the bile duct system. There may or may not be an associated infection (cholangitis). The obstruction may be a stricture, gallstone, or pancreatic carcinoma interfering with the common bile duct. The liver is a deep green color and of normal size or slightly enlarged. Its surface is smooth or only finely granular. Intrahepatic bile ducts are dilated and often contain neutrophilic leucocytes. Microscopically, inspissated masses of bile distend the bile canaliculi, and there is increased connective tissue in portal areas and around the periphery of the lobules. Chronic inflammatory cells, mainly lymphocytes and plasma cells, infiltrate this fibrous tissue.

Pigment Cirrhosis.—The liver changes in hemochromatosis may be referred to as pigment cirrhosis. The gross and microscopic features of the liver are those of a mild portal cirrhosis with the addition of large amounts of hemosiderin pigment (see p. 49).

Syphilitic Cirrhosis.—The liver is commonly involved in congenital syphilis, and many spirochetes may be demonstrable in that organ. In some cases there is a diffuse fibrosis within the lobules (see Fig. 43). In acquired syphilis the liver is not so regularly affected, but gummas may occur, which heal by fibrous scars and leave a marked distortion of the organ (hepar lobatum).

Cardiac or Congestive Cirrhosis.—Long-continued chronic passive congestion of the liver leads to atrophy of liver cells around the central vein areas, with a relative increase in the connective tissue. There may be also a diffuse fibrosis and alteration of architecture. It is most commonly associated with constrictive pericarditis and rheumatic heart disease.¹⁸

Parasitic Cirrhosis.—Due to the lodgment of ova in the liver, cirrhosis may be produced by infection with *Schistosoma mansoni*, and less frequently with *S. japonicum* and *S. haematobium*. Dense whitish zones of fibrosis develop about intrahepatic portal branches. The external surface

may be nodular, and similar in gross appearance to a Laënnec's cirrhosis. Small fibrous nodules, a millimeter or two in diameter, may be scattered through the liver. Microscopically, the ova or remains of their shells may be found in the fibrous areas. Brownish pigment granules are held in Kupffer's cells. Splenomegaly, ascites, and esophageal varices develop in late stages¹⁹ (see page 177).

The liver fluke, *Clonorchis sinensis*, may produce a biliary type of cirrhosis, due to lodgment in biliary channels. There is fibrous thickening and dilatation of bile ducts, and fibrosis and cellular infiltration in the portal spaces. Flukes or their remnants may be found in involved areas.⁹

Weil's Disease

Weil's disease, or spirochetel jaundice, is due to infection with *Leptospira icterohemorrhagiae* and affects particularly the kidneys, liver, capillaries, and skeletal muscles (see p. 147). The liver is usually enlarged and bile stained. Microscopically one sees degeneration and inflammation of liver structure. Areas of necrosis may be slight and focal, or so extensive as to simulate acute yellow atrophy. Biliary stasis is evident in the central part of the lobule. There may be some evidence of proliferation of hepatic cells.²⁰

Abscess of the Liver

Abscesses of the liver may be (1) pyogenic, (2) amebic, and (3) actinomycotic.

Pyogenic abscesses may result from: (a) spread of organisms to the liver by way of the portal vein (pylephlebitis) from the appendix, rectum, or other parts of the bowel; (b) extension of organisms to the liver by way of the bile ducts (cholangitis) from the gall bladder; (c) spread to the liver from contiguous infected tissue, e.g., a subphrenic abscess; (d) infection carried to the liver by hepatic arteries in septicemia; and (e) penetrating traumatic injuries. The bacteria most commonly found are *B. coli*, staphylococci and streptococci.²¹

Pylephlebitis with multiple liver abscesses most frequently is an extension from an acute suppurative appendicitis. The abscesses are more abundant in the right lobe. The areas of necrosis vary from microscopic size to a diameter of several centimeters and by coalescence can form large cavities. Necrosis, cellular disintegration, and leucocyte accumulation are found in the areas of abscess.

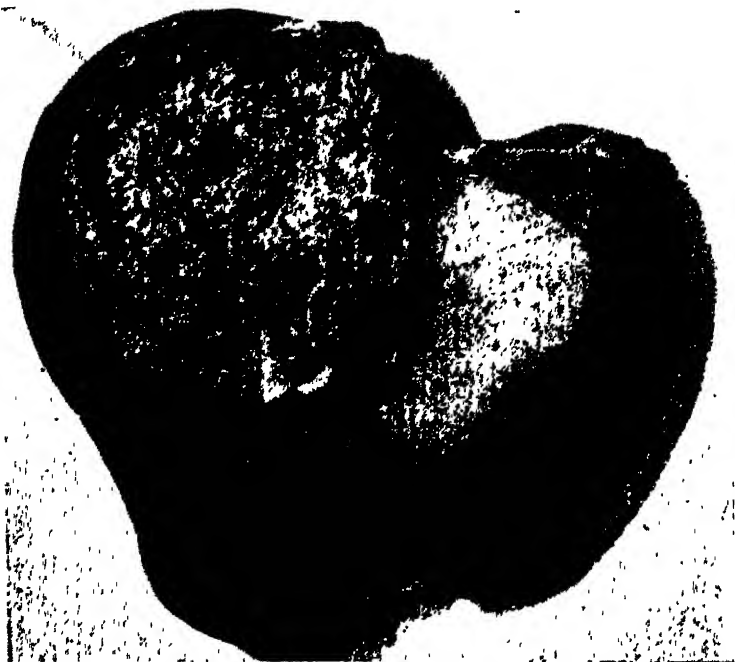


Fig. 180.—Amebic abscess of liver. (Courtesy Dr. H. C. Schmeisser.)

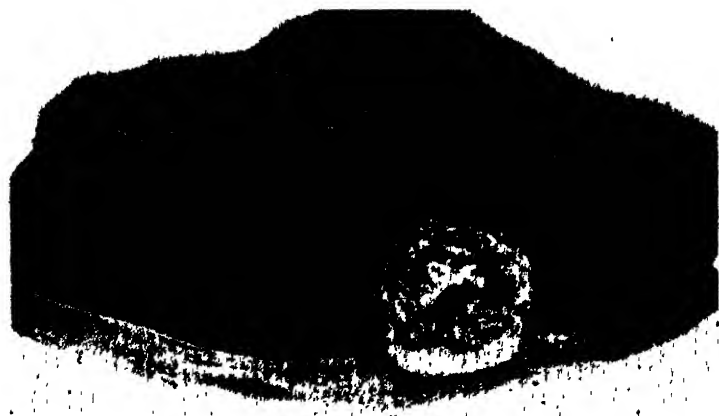


Fig. 181.—Echinococcus cyst of liver. Note the convoluted membranous content. (Courtesy Dr. H. C. Schmeisser.)

Occasionally there is the complication of rupture or spread of the infection to adjacent tissues. **Pyogenic hepatic abscesses** due to spread of organisms to the liver by the hepatic arteries are usually but part of a general septicemia, and abscesses are present in other organs as well.

Amebic abscess (tropical abscess) is due to spread of *E. histolytica* from intestinal lesions by way of the portal vein. The lesion begins in the portal areas, with lysis of tissue and but little accompanying inflammatory reaction. Adjacent abscesses coalesce to produce lesions of considerable size. The larger abscesses tend to become walled off by connective tissue²² (see page 162).

Actinomycotic abscesses of the liver are the result of spread from intestinal lesions by way of the portal blood. Multiple small ragged abscess cavities are produced, in which the actinomycotic colonies can be found (see p. 154).

Cysts of the Liver

Cysts in the liver are commonly of the following types: (1) hydatid (ecchinococcus) cysts; (2) cystic distention of ducts (hydrohepatosis); and (3) congenital cysts.

Hydatid cysts are due to the lodging in the liver of the larval form of the dog tapeworm, *Taenia echinococcus* (see p. 180). The liver is a commonly involved organ. The cyst wall is composed of concentric hyaline laminae, lined by germinal cells from which grow "daughter" cysts. Scolices and hooklets of the worm may be identified in the cyst wall or its contents by microscopic examination. Old cysts, in which the parasites are dead, contain a yellowish-gray, putty-like material.

Cystic distention of bile ducts (hydrohepatosis) is the result of obstruction to bile passages, particularly if such obstruction is intermittent, incomplete, or slow in development.

Congenital cysts are not common but sometimes are found associated with a congenital cystic condition of the kidneys. They are usually small and cause no disturbance.

Tumors of the Liver

Hemangioma.—The most common tumor of the liver is a cavernous hemangioma, similar to those occurring elsewhere. At autopsy, it is often encountered as an incidental finding. It grows very slowly or remains stationary in size.

Adenoma.—Adenoma is relatively infrequent. It is a circumscribed mass of well-formed liver cells which grows expansively, compressing the surrounding liver substance. Bile duct adenoma also occurs, and tends to be cystic.



Fig. 182.—Portal cirrhosis and carcinoma (hepatoma) of liver. (Courtesy Dr. H. C. Schmeisser.)



Fig. 183.—Carcinoma of liver (hepatoma) with cirrhosis. The cut surface of the liver shows the multiple tumor masses. (Courtesy Dr. H. C. Schmeisser.)

Carcinoma.—The liver is a very common site for metastatic tumors, whereas *primary carcinoma* is relatively uncommon, occurring in 0.3 to 1 per cent of autopsies. In the Orient it is more common, particularly in South China, where there is a high incidence of infection with the liver fluke. Cancer of the liver occurs at all ages, even in young infants, but the highest incidence is between fifty and sixty years. A considerable proportion is associated with cirrhosis. The incidence is much higher in males than in females.⁴¹



Fig. 184.—Metastatic carcinoma in liver. (Primary in large intestine.)
(Courtesy Dr. H. C. Schmeisser.)

There are three gross forms: (1) nodular, in which various circumscribed tumor nodules are present throughout the liver; (2) massive, in which a single large tumor occupies one of the lobes; and (3) diffuse, in which the tumor cells are found extensively invading every part of the liver.

Histologically there are two types, hepatoma and cholangioma, but some highly undifferentiated tumors are difficult to classify. **Hepatoma** is more frequent and is composed of cells arranged in columns resembling normal liver cords. These cells are often hyperchromatic and multinucleated, or of giant size. Atypical lobules may be formed, and there is often some bile secretion. A delicate network of capillaries is

found in the stroma. **Cholangioma** is a glandular carcinoma arising from bile ducts. The columnar or cuboidal cells attempt to form tubules. The connective tissue stroma is dense and shows but few capillaries. Malignant cholangioma has a more rapid course than malignant hepatoma.

Intrahepatic spread is most common, but extrahepatic metastases are not unusual, particularly in regional lymph nodes and lungs. The symptoms are variable, multiple, and often appear unrelated, so that ante-mortem diagnosis is rarely accomplished.^{23, 24, 25}

THE GALL BLADDER

The gall bladder is a thin-walled sac, in which bile is concentrated by active mucosal absorption of water. The function of the gall bladder is as a reservoir for bile. The chief lesions of the gall bladder are inflammation, stone formation, and carcinoma. Inflammation (cholecystitis) is commonly due to bacterial infection, and it interferes with reabsorptive concentrating activity of the organ. Gallstones (cholelithiasis) are due to precipitation of constituents of bile. They may produce obstruction in the gall bladder, cystic duct, or common duct. Carcinoma is the only common type of tumor of the gall bladder.

Cholecystitis

Inflammation of the gall bladder may be acute or chronic. Most cases of cholecystitis are associated with bacterial infection. Chemical damage to the gall bladder wall due to the action of concentrated bile, promoted by obstruction of the cystic duct, may precede the bacterial infection.²⁶ The presence of stones also may promote an inflammatory process. Streptococci and *B. coli* are the organisms infecting the gall bladder most frequently. Infection may reach the gall bladder wall from the blood stream, by direct spread from adjacent organs, from the liver, or from the intestine through lymphatics, or by ascending bile ducts from duodenum.

In **acute cholecystitis** the gall bladder is enlarged, gray or reddish in color, and has a thick edematous wall. The mucosa shows areas of necrosis and ulceration, and leucocytes are present in the wall. Purulent exudate may fill the cavity (empyema of the gall bladder). Calculi are often associated with the inflammation and may obstruct the neck of the gall bladder, or they may erode through the softened and necrotic wall.



Fig. 185.—Chronic cholecystitis and cholelithiasis. Note the thickness of the wall of the gall bladder. The lowest stone is cut to show its radiating structure. (Courtesy Dr. H. C. Schmeisser.)



Fig. 186.—Cholesterolosis of gall bladder. Masses of lipoid are evident in the mucosal folds.

Chronic cholecystitis may be catarrhal, with merely slight thickening, lymphocytic infiltration and congestion of mucosal folds. In other cases, the changes are more marked, with areas of destruction of the mucosa, fibrous thickening of the wall, and a more diffuse infiltration of lymphocytes. Gallstones or duct obstruction often complicate a chronic cholecystitis.

Cholesterolosis

In cholesterolosis (strawberry gall bladder) multiple tiny, yellowish deposits of cholesterol are present in mucosal folds. These yellow areas on the reddish background of a congested

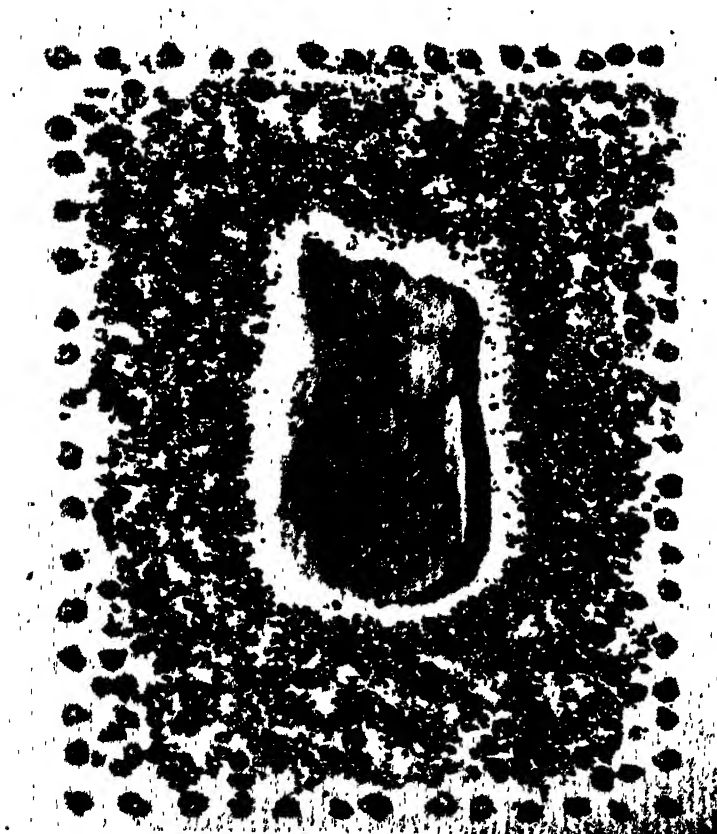


Fig. 187.—Chronic cholecystitis and cholelithiasis. The gall bladder contained more than 4,000 stones. (Courtesy Dr. H. C. Schmeisser.)

mucosa suggest the appearance of a ripe strawberry. There is usually an associated increase of cholesterol in bile and blood. Cholesterosis is often of little significance, but it may be associated with chronic inflammation in the gall bladder wall. Pedunculated mucosal folds containing cholesterol sometimes are pinched off and form the nuclei of stones.

Cholelithiasis

The several types of gall bladder calculi, which have a distinctive etiology and appearance, are cholesterol stones, pigment stones, mixed stones, and calcium carbonate stones. The important factors in their formation are disturbances of cholesterol metabolism, infection, and stasis.



Fig. 188.—Cholecystitis and cholelithiasis. Note the multiple faceted calculi. (Courtesy Dr. H. C. Schmeisser.)

Types of Gallstones.—The cholesterol stone is usually single. It is a large white calculus, light in weight, soft, and has a radiate structure evident on its cut surface. It occurs in the absence of infection and is probably of metabolic origin. The formation of a cholesterol stone appears to be influenced by hypercholesterolemia, dietary disturbances, diabetes, pregnancy, etc. Low bile salt concentration in

TABLE IX
CHARACTERISTICS OF GALLSTONES

TYPE OF STONE	CAUSE	SIZE	NUMBER	COLOR	CON-SISTENCY	OUTER SURFACE	CUT SURFACE	EFFECTS
Cholesterol	disturbed cholesterol metabolism	large	single	white or white covered by yellow or brown	soft	smooth	radiating crystalline structure	rarely cause obstruction
Pigment	excessive bilirubin production	small	multiple	very dark	soft or brittle	rough	amorphous	often found in bile ducts
Mixed	infection	small or large	multiple	dark brown, reddish black, or green	hard	rough, faceted	laminated	often cause obstruction
Calcium carbonate	stasis	variable	single or multiple	white	soft	nodular	amorphous	

gall bladder bile decreases the ability of cholesterol to remain in solution, and thus favors precipitation. Inflammation of the gall bladder may influence this by causing abnormal absorption of bile salts. Disturbances in absorptive and secretory functions of the gall bladder promoted by neurogenic and hormonal factors have been thought to favor calculus formation.²⁶ The solitary large cholesterol stone may give rise to few or no symptoms and is usually too large to enter and obstruct ducts.

Pigment stones, composed essentially of bilirubin, are multiple, small, dark brown or black, hard and brittle. Formed by precipitation of bile pigment in an uninfected gall bladder, they are associated with conditions having increased bilirubin concentration of the bile, such as hemolytic jaundice or pernicious anemia. Stasis favors their formation.

Mixed stones, also called infective or mulberry stones, are hard, rough-surfaced stones composed of mixtures of bilirubin, cholesterol, calcium, and some organic material. They are usually multiple and sometimes are present in huge numbers. Adjacent surfaces may be faceted. They are composed of concentric laminae, laid down on a nucleus of organic material. Mixed stones are the common type of calculus associated with infection of the gall bladder. "Combined" stones also may develop, and have a nucleus of a mixed stone, and a shell of cholesterol or pigment.²⁷

Calcium carbonate stones are rare, soft, white stones, usually formed only when there is complete obstruction of the cystic duct. Stasis is a factor in deposition of bile pigment and calcium. The more complete the obstruction, the greater the proportion of calcium, which is deposited from the gall bladder wall.

Effects of Gallstones.—Biliary calculi may produce injury in three ways: (1) their presence causes continuation of a chronic inflammatory process; (2) the chronic irritation of calculi may be a factor in the development of carcinoma of the gall bladder; (3) stones may cause obstruction at the neck of the gall bladder or in the bile ducts.

The effects of obstruction of bile passages depend on the site and completeness of the obstruction. Large stones such as the solitary cholesterol calculus are often too large to get into bile ducts, though they may obstruct the neck of the gall bladder. Passage of a small calculus distending biliary ducts elicits the severe pain of biliary colic.

Complete obstruction of the neck of the gall bladder or cystic duct leads to hydrops or mucocele of the gall bladder,

in which condition the pigmented bile has been absorbed and replaced by a mucoid secretion from the lining of the gall bladder. Obstruction by a stone in the common duct results in but little distention of the gall bladder if the wall has been thickened by inflammation, although bile passages themselves are usually visibly dilated above the obstruction.



Fig. 189.—Carcinoma of the gall bladder. Papillary adenocarcinoma of the fundus and cholelithiasis. (Courtesy Dr. H. C. Schmeisser.)

Courvoisier's law states that obstruction of the common bile duct by pressure from the outside, as by a carcinoma of the pancreas, produces a distended gall bladder, whereas obstruction by a stone produces little or no distention of the gall bladder. The usual explanation is that in the latter instance the gall bladder wall is thickened and contracted as a result of inflammation.

If biliary obstruction is present for a considerable time, the bilirubin excretory function of the liver may become suppressed, and a watery or mucoid fluid, the so-called "white bile," is found in bile ducts.

The pancreas may be affected when a stone is impacted in an ampulla of Vater which acts as a common opening of pancreatic and bile ducts. In such a case reflux of infected bile into the pancreatic duct may give rise to acute pancreatitis (see p. 404).

Carcinoma of the Gall Bladder

The only important tumor of the gall bladder is carcinoma. About 75 per cent of cases occur in women, commonly between 50 and 70 years of age. More than 65 per cent of carcinomas of the gall bladder are associated with calculi, which are often thought to have some causative role, probably by mechanical irritation.

Cancer of the gall bladder is commonly an adenocarcinoma, but occasionally of squamous cell type. Adenocarcinoma may be subdivided into (a) an infiltrating scirrhus type, (b) a papillary type, and (c) a mucous type. The **infiltrating scirrhus** type is most common; it forms a firm tumor which spreads widely through the gall bladder wall, causing it to be greatly thickened. The lumen is narrowed and eventually obliterated. Microscopically it is an infiltrating adenocarcinoma, often with abundant dense fibrous stroma. The **papillary adenocarcinoma** forms a friable fungating tumor which grows into the lumen of the gall bladder. Microscopically it presents stalks of connective tissue stroma covered by atypical columnar epithelium and infiltrated by glandular acini. The papillary type is less malignant and slower in its growth and spread than is the infiltrating adenocarcinomatous variety. The **mucoid adenocarcinomas** form a bulky gelatinous mass, in which the tumor cells are distended with mucoid material and may have a "signet ring" form. **Squamous-cell carcinoma** of the gall bladder is a rare variety assumed to arise on the basis of metaplasia of the epithelial lining.

Spread of cancer of the gall bladder is by direct extension to the liver, and metastasis to regional lymph nodes. Further spread may occur by lymphatic and blood stream metastasis, but widespread extension is not the usual occurrence.

THE PANCREAS

Acute Pancreatitis

Acute pancreatitis occurs in two forms which are similar in clinical manifestations but have radically different pathologic changes and prognoses. There are in each sudden severe epigastric pain, prostration, shock, and toxicity. The serum amylase (diastase) is high in early stages.³⁰

In the benign form, sometimes referred to as acute interstitial pancreatitis, there is only marked edema of the pancreas and peripancreatic tissues, and the condition subsides without serious effects.³¹ The more serious form frequently is associated with severe hemorrhage or massive necrosis. It may be termed acute hemorrhagic pancreatitis or acute pancreatic necrosis when hemorrhage or necrosis respectively is the outstanding feature. Liberated trypsin acting on blood vessel walls accounts for the hemorrhagic feature. Liberation of lipase results in a digestion of fatty tissue (fat necrosis), the affected fatty tissue having a characteristic appearance.

Pathogenesis.—The causes of acute hemorrhagic pancreatitis are varied, but probably the most common cause is reflux of bile into the pancreatic duct. In 80 to 90 per cent of individuals there is a common opening of the biliary and the pancreatic ducts into the duodenum. Reflux of bile may occur by creation of a common biliary and pancreatic channel due to spasm of the sphincter of Oddi in chronic disease of the biliary tract.³¹ Less commonly it is due to impaction of a small biliary calculus at the ampulla of Vater. In other cases, acute pancreatitis may be due to direct spread of infection from neighboring tissues, to vascular disease or occlusion, or to pancreatic duct obstruction.

When the pancreatitis is due to infection or vascular interference, the condition may be of a milder, subclinical grade, and lead to recovery with scarring or chronic pancreatitis. Pancreatic vessels are occasionally involved in the severe arteriolar degeneration and necrosis of malignant hypertension, but the resulting acute pancreatitis is usually overshadowed by the severe renal involvement.

The more severe hemorrhagic and necrotic forms of acute pancreatitis may be due to obstruction of pancreatic ducts



Fig. 190.—Fat necrosis and acute pancreatitis. The white opaque areas represent fat necrosis. A small white rod is in the duct opening into the duodenum. (Courtesy Dr. H. C. Schmeisser.)



Fig. 191.—Fat necrosis of pancreas.

as a result of metaplasia of lining epithelium as has been demonstrated by Rich and Duff.²⁹ Such obstruction occasionally leads to rupture of acini and release of trypsin, which in turn affects blood vessel walls and produces hemorrhage. Ingestion of alcohol or a heavy meal may be a contributory factor, by stimulation of pancreatic secretion.

Pathologic Appearance.—The pancreas is enlarged and firm, with softer friable areas of necrosis. Various degrees of hemorrhagic and gangrenous changes may involve portions of the pancreas or the whole organ. The gangrenous changes progress rapidly post mortem. Areas of fat necrosis affect the fat of the pancreas, mesentery, and omentum. These appear as firm, dry, opaque yellow or gray nodules. The necrotic areas of fatty tissue are surrounded by a zone of hyperemia and leucocytes.

Chronic Pancreatitis

Chronic pancreatitis is manifested by fibrosis and increased firmness of the organ. The fibrosis may be interlobular or interacinar. The latter type sometimes involves islets and may be associated with diabetes. Dilatation of acini with appearance of a central space or channel indicates some duct obstruction, as does also the presence of inspissated material in the lumen of ducts.

Pancreatic Calculi

Calculi in pancreatic ducts are the result of inflammation. They are single or multiple, composed mainly of calcium phosphate or calcium carbonate, and may cause duct obstruction. They are uncommon.

Pancreatic Cysts

True cysts in the pancreas may be congenital or due to duct obstruction. Pseudocysts result from degeneration and softening of tissue, or from hematomas. Some pancreatic tumors are cystic.

Fibrocystic Disease

Pancreatic insufficiency in early life is the result of obstruction of the ducts and acini, in which inspissated secretion can be seen. This leads to dilatation of ducts, atrophy of the parenchyma, and fibrosis. Deficiency of pancreatic juice in the neonatal period appears to be associated with meconium ileus. At a later period in infancy, the pancreatic deficiency

results in poor digestion and deficient absorption of starch, fat, and fat-soluble vitamins, simulating the celiac syndrome. Respiratory infections are usually present in addition to the intestinal disturbance. Vitamin A deficiency may be a feature.³²

The pancreas may show little gross change except to be firmer and thinner than normal. Microscopically, the exocrine parenchyma is atrophic and scanty, with a relative increase of the fibrous stroma, which may be infiltrated by some lymphocytes and mononuclear cells. Inspissated eosinophilic material may be found in dilated acini and ducts. Fatty replacement of atrophic parenchyma may occur as well as fibrosis. The islets of Langerhans remain intact. Bronchopneumonia, bronchitis, and bronchiectasis are the common lesions in the lungs.

Farber³³ has suggested that the condition may be a systemic disease, the primary fault being an alteration of the character of the secretions within glandular structures. Evidences of disturbed secretion may be found also in the respiratory tract, upper intestinal tract, liver, and gall bladder.

Diabetes Mellitus

Diabetes mellitus is a disease due to insufficient production of the hormone, insulin, by the islets of Langerhans of the pancreas. This, in turn, gives rise to a disturbance of carbohydrate metabolism, with inability to store glycogen in the liver, excessive accumulation of glucose in the blood (hyperglycemia), and excretion of the excessive sugar in the urine (glycosuria). Fat metabolism also is upset. The fats cannot be completely oxidized, ketone bodies accumulate, and acidosis results. Clinical features are excessive appetite, thirst, and urination. In older individuals, obesity and severe arteriosclerosis are common accompaniments.

The relation of the pancreatic islets to diabetes has been proved by extirpation of the organ, which results in diabetes, and by the isolation of the hormone, insulin, from the islets after selective atrophy of the acinar tissue. Injection of insulin will control most cases of diabetes. Special methods of fixation and staining will demonstrate α and β granular cells in the islets, and the β cells are believed to be active in insulin production.³⁴

There appear to be two main causes of diabetes: in one the β cells are damaged and produce very little insulin; in the other the β cells are normal, but owing to some interfering substance, they fail to produce sufficient insulin. There

is evidence that the interfering substance is of pituitary origin. In these latter cases no histologic change may be evident in the islets. In the rare cases of diabetes that are resistant to insulin therapy, there is usually hepatic injury or disease.

Alloxan, the ureide of mesoxalic acid, has been found to produce a specific necrosis of the islets of Langerhans in experimental animals, and to result in diabetes mellitus.³⁹ The islet tissue of man has a greater resistance, but it appears possible to produce some decrease of function of islet cell tumors.⁴⁰

The anatomic changes in diabetes mellitus to be considered are: (1) the lesions in the pancreas, and (2) the lesions in other organs resulting from the disturbed metabolism.

Lesions in the Pancreas.—No characteristic or common gross change involves the pancreas. Occasionally a massive destruction of pancreatic tissue, as by acute or chronic pancreatitis, malignant tumor, or hemochromatosis, may result in diabetes. Ordinarily, however, there is sufficient reserve of insulin-producing power that destruction of even a large proportion of the pancreas may not result in diabetes.

In a series of 842 cases of diabetes mellitus the following were the findings in the pancreatic islets³⁵:

Approximate per cent

19	-----	no lesion
34	-----	hyalinization of the islets
31	-----	fibrosis
8	-----	hypertrophy of islets
2.5	-----	hydropic degeneration
2.5	-----	pyknotic nuclei
1.5	-----	hemochromatosis
1.5	-----	lymphocytic infiltration

Hyaline degeneration of the islets, which is a common change in elderly and mild diabetics, and also fibrosis of islets, may be found in individuals who have not suffered from diabetes. In some cases the hyaline material in the islets appears to be a type of amyloid.³⁶

Lesions in Other Organs.—Pathologic changes in organs other than the pancreas depend on the disturbed metabolism and are mainly changes in the distribution and amount of glycogen in certain tissues.³ Such changes will not be present in cases in which the metabolic disturbance is controlled by insulin administration. Glycogen may be demonstrated in tissues by prompt fixation in alcohol, and staining

by Best's carmine. The glycogen appears as a bright red intracellular material.

The kidney contains excessive glycogen in the epithelium of Henle's loops and occasionally in convoluted tubules. The cells have a water clear cytoplasm, or hydropic appearance. This change may be associated with glycosuria from any cause. Intercapillary glomerulosclerosis is a glomerular lesion frequently associated with diabetes mellitus (see p. 295).

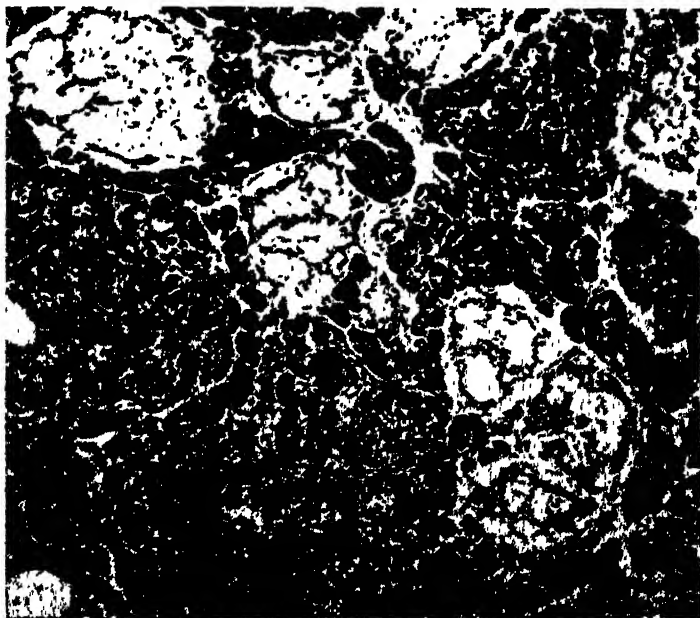


Fig. 192.—Hyalinization of islets of Langerhans of pancreas. From a case of diabetes mellitus.

The liver has decreased glycogen storage within cytoplasm of the liver cells, although the nuclei of the liver cells may have increased glycogen content, and appear clear and glassy. Skin, voluntary muscle, and heart may also show some changes in glycogen content.

Tumors of the Pancreas

Primary tumors of the pancreas may be carcinoma, arising from duct or acinar tissue, or adenoma, arising from cells of the islets of Langerhans.

Carcinoma of the Pancreas.—The majority of carcinomas of the pancreas arise in the head of the organ, where early in their course they cause obstruction of the common bile duct. The obstruction produces dilatation of bile ducts and gall bladder, and clinically gives rise to a painless, ever-deepening jaundice. Spread to neighboring tissue and by metastasis is a late feature. In the less common tumors arising in the body or tail, earlier and more widespread extension and metastasis result in a greater variety of clinical symptoms.⁴¹

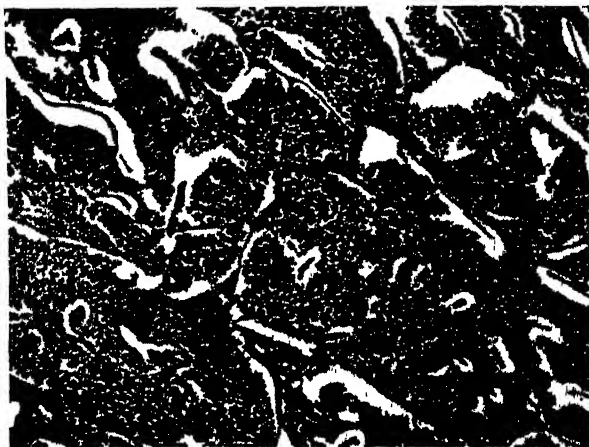


Fig. 193.—Islet cell adenoma of pancreas.

The tumor forms a hard nodular mass within the pancreatic tissue, often fibrous or scirrhous in character, and difficult to distinguish grossly from chronic pancreatitis. Microscopically, it may be a cylindrical cell adenocarcinoma originating from the pancreatic duct system, or less frequently an acinar cell type, resembling the parenchyma of the pancreas.

Islet Cell Tumor of the Pancreas.—Tumors composed of functioning islet tissue occasionally occur in the pancreas. They produce excessive hormone, giving rise to the clinical picture of hyperinsulinism, with marked hypoglycemia. Paroxysmal attacks rather than continuous hyperinsulinism is the usual form of disturbance. Removal of the tumor relieves the symptoms.

The islet cell tumor is a benign adenoma, but rarely there may be evidence of malignancy. Its derivation is probably from duct epithelium, which may differentiate into either islet tissue or acinar tissue. The tumors vary markedly in size and gross appearance, but microscopically they closely duplicate the appearance and architecture of normal islet tissue, so that structurally they are simply gigantic islets of Langerhans. Most of the cells are comparable to the beta cells of normal islets. Degenerative changes such as fibrosis, hyalinization, and calcification, which commonly affect islets, may also be found in the tumor. The presence of the functioning tumor apparently does not suppress the secretory activity of the normal islets. A few adenomas have been reported in heterotopic pancreatic tissue.⁴²

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CHAPTER XVI

THE RETICULO-ENDOTHELIAL SYSTEM, SPLEEN, AND LYMPH NODES

THE RETICULO-ENDOTHELIAL SYSTEM

The reticulo-endothelial system is composed of widespread cells having the essential and common ability to phagocytose particulate foreign material, such as injected vital dyes or India ink. Some of these phagocytic cells are endothelial cells lining the blood sinuses of the spleen, liver, and bone marrow and the lymph sinuses of lymph nodes. But also, all connective tissues contain elements (undifferentiated mesenchymal cells), which are capable of assuming mobility and phagocytic function. These cells go under the terms of histiocytes, clasmatocytes, polyblasts, resting wandering cells, adventitial cells, etc. Both the endothelial cells and the undifferentiated mesenchymal cells are capable of becoming macrophages.

The conception of the reticulo-endothelial system has been furthered by Maximow, who pointed out that in the spleen, bone marrow, and lymphatic tissue generally there exists an undifferentiated mesenchyme (called reticulum) in the form of a nucleated syncytium with an abundant meshwork of fibrils. These fibrils (reticulin) are not seen well in ordinary sections stained by hematoxylin and eosin. However, reticulin fibers are argyrophilic and are stained black by silver salts, which are converted to the black oxide. This syncytium or reticulum is not in itself phagocytic, but under stimulus of injury or inflammation there differentiates from it the mobile phagocytic macrophage. Since the undifferentiated mesenchyme is widespread throughout the body, macrophages likewise have diverse origin. Microglial cells are the corresponding phagocytic cells in the nervous system.

The monocyte of the circulatory blood is also phagocytic, and commonly believed of reticulo-endothelial origin. The other two main views regarding its origin are that it may arise from the lymphocyte or from the myeloblast. The ordinary lining endothelium of blood vessels and lymphatics, other than in the spleen, lymph nodes, liver, bone marrow, adrenal cortex, and hypophysis, is not actively phagocytic.

Reticulo-endothelial cells are important in normal breakdown of hemoglobin and formation of bile pigment, in fat metabolism, and in defense of the body. The blood is cleared of particulate matter, foreign material, and bacteria in its filtration through the liver, spleen, and bone marrow. The phagocytic cells ingest and remove dead tissue fragments, pigments, bacteria, fungi, and protozoa. For larger masses of particulate matter they fuse and form foreign body giant cells. The osteoclast of bone is a particular type of such a giant cell. The reticulo-endothelial system plays a role in immunity, and some evidence suggests that it has a function in antibody formation.

Diseases of the reticulo-endothelial system fall into three main groups: (1) Infections and inflammations in which proliferation and phagocytosis by reticulo-endothelial cells are prominent. Histoplasmosis and malaria are excellent examples. (2) Lipoidoses, or lipid storage diseases, in which, due to disturbed metabolism, fatty substances accumulate in reticulo-endothelial cells. The fatty material may be kerafin (Gaucher's disease), sphingomyelin (Niemann-Pick's disease), or cholesterol (Schüller-Christian disease, xanthomas). (3) Tumors and tumor-like conditions form a large and confusing group of conditions which includes the leucemias, Hodgkin's disease, reticulum-cell sarcoma, lymphoblastomas, and reticulo-endotheliosis.

Since the large storehouse of reticulo-endothelial cells is in the spleen, lymph nodes, bone marrow, and liver, the reticulo-endothelial involvement is considered in conjunction with diseases affecting these organs.

SPLEEN

The average normal adult spleen weighs 150 to 170 Gm., but the size and weight vary widely. Many of the diseases of the spleen bring about an enormous increase in its size and weight, sometimes to 2,000 Gm. or more. The adult spleen is usually not clinically palpable unless it weighs more than 300 Gm. The cut surface of the normal spleen is moderately firm, light red, and the Malpighian corpuscles are just visible as small grayish-white areas. Small accessory spleens are not uncommon. Microscopically, the discernible structures are (1) the Malpighian bodies (lymph follicles), which are cylindrical masses of lymphoid tissue surrounding small arteries; (2) the pulp, consisting of sinusoids separated by reticular tissue; and (3) trabeculae or fibromuscular bands which connect with the splenic capsule.

The spleen is not essential to life, but it has important functions, particularly as the main component of the reticulo-endothelial system. Thus it is important (1) in the breakdown of hemoglobin and formation of bile pigment, (2) in the filtration of organisms or other foreign material from the blood stream, (3) probably in the formation of antibodies and immunity, (4) as a reservoir for blood, and (5) for blood formation in the fetus or when there is severe anemia.

Splenectomy may be beneficial in rupture of the spleen, familial hemolytic jaundice, thrombocytopenic purpura, primary splenic neutropenia, and early stages of splenic anemia or Banti's syndrome.¹

Degenerative Conditions of the Spleen

Atrophy.—Reduction in size of the spleen may occur in old age, usually in association with marked arteriosclerosis of splenic vessels. Extreme atrophy may be present in late stages of sickle-cell anemia.

Arteriosclerosis.—Hyaline sclerosis of small arteries and arterioles in the spleen is very common, its frequency and severity increasing with age. While more pronounced when there is hypertension and arteriosclerosis is present elsewhere, the vascular change may be present in the spleen alone. When severe, it may cause multiple small infarcts or necroses in the spleen (spotted spleen—see below).

Amyloid.—The spleen is a common site for amyloid deposit (see p. 41).

Eosinophilia.—Allen² has pointed out that unusually large numbers of eosinophiles are found in the spleen in most cases of sudden death, as from trauma or coronary occlusion. The explanation is not known.

Pigmentation.—Pigment deposits in the spleen follow excessive breakdown of hemoglobin, due to hemolytic anemias (pernicious anemia, sickle-cell anemia), malaria, or chronic congestion (Banti's syndrome). Some brownish hemosiderin pigment in the spleen is a normal finding. In malaria, the pigmentation is excessive, so that the enlarged organ grossly exhibits a slate-gray color (see p. 166). In sickle-cell anemia and Banti's syndrome curious areas of fibrosis and pigmentation occur in the spleen (siderofibrotic nodules, Gandy-Gamna bodies, see pp. 417 and 441).

Multiple Necroses of the Spleen (Fleckmilz).—Speckling of the spleen may be due to widespread and irregular areas of necrosis as the result of confluence of many small infarcts.

The splenic arterioles commonly show marked degenerative changes with frequent thromboses. Most cases are associated with renal disease and uremia.^{3, 4}

Circulatory Disturbances in the Spleen

Infarction.—Infarction in the spleen is common and is usually the result of arterial embolism (see p. 60).

Congestion.—Chronic passive congestion in the spleen may be present in conditions of circulatory failure. The spleen is moderately enlarged and firm. Microscopically, the sinusoids appear dilated. Fibrosis occurs if the process continues for a long period.

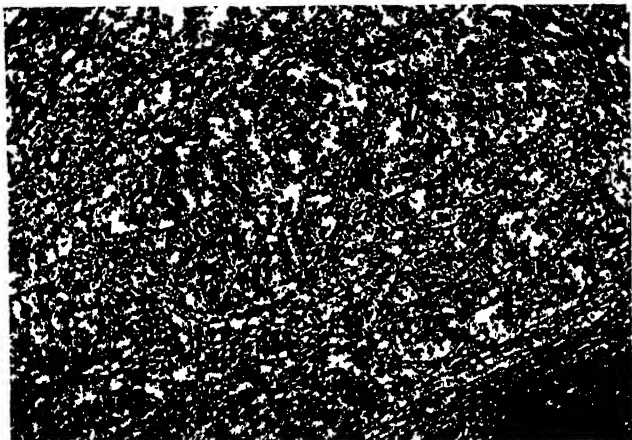


Fig. 194.—Chronic passive congestion of spleen. Note the dilated and congested sinusoids.

Chronic congestion is also associated with obstruction of the portal circulation (e.g., from cirrhosis of the liver) and with the Banti syndrome. Marked congestion of the spleen is a feature of sickle-cell anemia in its earlier phases, and of congenital hemolytic jaundice.

Banti's Syndrome (Hepatolienal Fibrosis).—Banti's syndrome is a symptom complex dominated by splenic enlargement, nonhemolytic anemia, and leucopenia. The splenomegaly is characterized by congestion and fibrosis, accompanied by portal hypertension, and often complicated in later stages, by ascites, hematemesis, portal cirrhosis of the

liver and thrombosis of splenic and portal veins.⁵ Splenectomy may be beneficial in early stages.

The spleen is markedly enlarged, averaging about 900 Gm. in weight. The capsule is thickened, and the cut surface is red, firm, and meaty in appearance. Microscopically the characteristic changes are (1) periarterial hemorrhages and (2) dilated venous sinuses. The hemorrhages may develop into areas of fibrosis or siderofibrotic nodules characterized by crystalline and amorphous deposits of iron-containing pigments, and iron incrustation of the connective tissue fibers. The distended sinusoids are usually the most obvious finding, their walls showing collagenous thickening.⁶ The size and relative number of lymph follicles per area are reduced.

Exactly the same type of splenic changes, but usually of less marked degree, accompany cases in which portal cirrhosis of the liver is a primary development. Various other disturbances in the portal circulation which obstruct the venous outflow of the spleen produce the same result.⁷ These conditions differ from Banti's syndrome only in that in the latter the splenic condition is considered primary. The term "splenic anemia" is often used in a broad sense to include the above conditions as well as others in which splenomegaly and anemia are prominent features.⁸

Rupture of the Spleen.—Rupture of the spleen is usually the result of direct trauma over the splenic area. Unless there is prompt operation, fatal intra-abdominal hemorrhage usually results.

Inflammations of the Spleen

Acute Splenitis (Acute Splenic Tumor).—Splenic reaction with moderate enlargement accompanies acute systemic infections, particularly bacteriemias or septicemias. In such cases the causative organisms are usually obtainable in cultures from the spleen. Rich⁹ has presented evidence that acute splenic tumor represents a reaction to the presence of foreign protein, whether bacterial or nonbacterial.

Two forms occur, a gray or "septic" type, and a red or "typhoid" type. In the gray type of acute splenitis the spleen is moderately enlarged and very soft. On the cut surface the soft swollen pulp has a grayish color, with a purplish tinge. The tissue is so soft as to be almost fluid, and it is easily scraped away with a knife. The red type occurs with bacillary infections, such as typhoid fever. The enlarged soft spleen is very red from intense congestion.

Microscopically the changes in acute splenitis are congestion and cellular accumulation in the pulp. In some cases many of the cells are polymorphonuclear leucocytes, but commonly they are large basophilic mononuclear cells which are lymphoid in character.⁹

Tuberculosis.—The spleen is usually involved in generalized miliary tuberculosis. In rare cases, a large localized tuberculous lesion develops in the spleen, while the original focus remains quiescent or heals. Small rounded hyalinized fibrous nodules, 1 to 3 mm. in diameter, are a frequent finding in the spleen and in most cases represent healed tubercles.

Malaria.—The spleen is enlarged and heavily pigmented in malaria (see p. 166).

Histoplasmosis.—The spleen is often greatly enlarged in histoplasmosis, due to marked proliferation of reticulo-endothelial cells. The small organism can be seen in the cytoplasm of these phagocytic cells (see p. 157). Similar splenic lesions occur in kala-azar.

Cysts and Tumors of the Spleen

Cystic cavities in the spleen are rare. Most are pseudocysts resulting from encapsulation of an area of hemorrhage or degeneration in the pulp. Epidermoid cysts and parasitic (hydatid) cysts are rare occurrences.¹⁰

Tumors of the spleen, either primary or metastatic, are rather uncommon. Hemangioma, although rare, is the most frequent primary tumor. The reason for the rarity of metastatic tumors in the spleen is not known.

LYMPH NODES

The lymph nodes are focal collections of lymphoid and reticulo-endothelial cells. Lymphoid tissue is widely distributed in other tissues as well, such as the alimentary canal and spleen. The main elements in lymph nodes are (1) lymph follicles (germinal centers) supposedly the site of formation of lymphocytes; (2) lymph sinuses, lined by endothelium, and (3) the medulla or pulp consisting of lymphocytes and reticulum cells in a delicate meshwork of reticulin fibers.

The lymph nodes are an integral part of the reticulo-endothelial system and participate in its diseases. The main lesions of lymph nodes are inflammations (lymphadenitis) and tumors (primary and metastatic).

Lymphadenitis.—Acute lymphadenitis occurs in lymph nodes draining an area of acute inflammation, e.g., in cervical lymph nodes in acute infections of the throat or in axillary lymph nodes in infections of the hand or arm. The lymph nodes are swollen and tender, and in pyogenic infections suppuration may occur. Microscopically, the sinuses of the lymph nodes are found filled by polymorphonuclear leucocytes or mononuclear cells. In certain infections the lesions in lymph nodes are of a characteristic nature, e.g., in tularemia, lymphogranuloma venereum, and tuberculosis. In disseminated lupus erythematosus the lymph nodes are enlarged in 66 per cent of cases, showing edema, engorgement, and, sometimes, necrosis.

Chronic lymphadenitis, which may be found in nodes draining an area of low-grade inflammation, shows proliferation of mononuclear cells which fill the sinuses. Fibrosis usually does not occur.

Infectious Mononucleosis (Glandular Fever).—Infectious mononucleosis is a benign condition, occurring most frequently in young adults, characterized by slight enlargement of superficial lymph nodes, sore throat, mild fever, increase in mononuclear cells (probably of lymphoid origin) in the blood, and a positive heterophile antibody (Paul-Bunnell) test (the serum in high dilution, i.e., a titer of 1:160 or more, agglutinates sheep's red cells). The disease may be mistaken for lymphatic leucemia. The mortality is almost nil,¹¹ but fatality has occurred due to rupture of the spleen.¹²

The lymph nodes show a maintenance of architecture (albeit distorted) with distinguishable lymph sinuses and germinal centers. Throughout the pulp, in the sinuses, and on the edges of the germinal centers are large numbers of the specific large mononuclear cells, identical with those in the circulatory blood. Marked proliferative activity is evident in the pulp.¹³

In addition to involvement of lymphoid tissues of the lymph nodes, spleen, tonsils, and bone marrow, there may be focal areas of mononuclear infiltration, reticulocyte proliferation, and necrosis in the liver, kidneys, and lungs.¹²

Acute Infectious Lymphocytosis.—Under the term "acute infectious lymphocytosis" Smith¹⁴ and others have described an infectious and contagious condition in children characterized by a relative and absolute lymphocytosis of small lymphocytes of normal appearance. Clinical signs are often only mild constitutional reactions, and the outcome is favorable. The white cell count of the blood may be from 15,000

to 60,000 per cu. mm., and up to 90 per cent lymphocytes. Biopsied lymph nodes show a marked proliferation of the reticulo-endothelium of the sinuses and hyaline degenerative changes in the lymph follicles. Acute infectious lymphocytosis is differentiated from leucemia and infectious mononucleosis by the normal appearance of the predominating small lymphocytes and the negative heterophile agglutination reaction.

Metastatic Tumors.—Carcinomas particularly tend to metastasize to regional lymph nodes. The tumor cells are first seen in the sinuses of the periphery or pulp, but lymphoid tissue eventually is replaced by tumor and invasion occurs through the capsule.

TUMORS OF THE RETICULO-ENDOTHELIAL AND LYMPHOID TISSUES

Apart from the infections in which proliferation of reticulo-endothelial cells is a marked feature (malaria, histoplasmosis, kala-azar) and the lipoid storage diseases (Gaucher's disease, etc.), there occurs a variety of tumors and tumor-like conditions involving lymphoid and reticulo-endothelial structures. Being of obscure causation, etiologic classification fails. The following simplified morphologic classification should be viewed with the realization that gradations and overlappings preclude sharp lines of distinction.

I. Reticulo-endotheliosis

II. Lymphoblastomas

1. Follicular lymphoblastoma
2. Lymphosarcoma (a) small cell type—malignant lymphocytoma
(b) large cell type—reticulum-cell sarcoma
3. Hodgkin's disease
4. Mycosis fungoides (see p. 638)
5. Lympho-epithelioma (see p. 458)

III. Leucemias (see p. 445)

1. Lymphocytic
2. Myelocytic
3. Monocytic

Reticulo-Endotheliosis

Reticulo-endotheliosis (reticulosis, aleucemic reticulosis) is a rare condition in which there is diffuse hyperplasia of the reticulo-endothelial system to the point of replacement

of normal structures. It may occur at any age but is more frequent in infants and young children. The characteristics include splenomegaly, hepatomegaly, anemia, purpura, and bony changes such as areas of rarefaction and cyst formation. A fatal ending is reached in two weeks to two years, usually from acute infection.

The most marked changes are found in the spleen, lymph nodes, liver, and bone marrow. The enlarged spleen shows scattered indefinite grayish-yellow nodules on the cut surface, and similar nodules may be seen in the liver. Microscopically, there is a great proliferation of large mononuclear cells in organs of the reticulo-endothelial system, with distortion of normal structure. These cells are rounded or polyhedral and some may be very large (up to 50 microns). Multinucleated giant cells may be seen. Occasional mitoses are present. Silver staining shows a proliferation of reticulin fibers in contact with the atypical cells.

Reticulo-endotheliosis is closely related to monocytic leukemia and Hodgkin's disease. By some observers it is considered simply an aleucemic form of monocytic leukemia. However, the rarefaction of bone and formation of bone cysts appear characteristic of reticulo-endotheliosis, and in monocytic leukemia the cell type is more uniform, the process more widespread, and with the appearance of infiltration rather than of hyperplasia *in situ*.^{15, 16}

In monocytic leukemia there is hyperplasia of the reticulo-endothelial tissues, with enlargement of the spleen, liver, and often lymph nodes. The bone marrow is almost always involved. A tendency to hemorrhage, ulceration, and necrosis is prominent, the oral cavity being the commonest site of such involvement. Infiltration with monocytes and a general reticulo-endothelial hyperplasia is the main microscopic finding, evident particularly in the spleen, liver, lymph nodes, bone marrow, and skin. Areas of necrosis and hemorrhage are also common in these tissues. In chronic cases the microscopic appearance may simulate that of Hodgkin's disease, with eosinophiles and Reed-Sternberg cells.¹⁸

Follicular Lymphoblastoma

Follicular lymphoblastoma (follicular reticulosis, giant follicular lymphadenopathy) is a relatively benign disease of lymph nodes and spleen, in which the characteristic feature is a marked increase in number and size of lymph follicles. It occurs in adults, the average age being above forty. The blood picture is normal and constitutional symp-

toms are mild. Ascites is a common accompaniment. The lymph nodes are involved and usually the spleen as well, but the tonsils and intestinal lymphoid tissues are unaffected. The tissue is peculiarly radiosensitive, and the prognosis is for longer survival than in most other lymphomatous diseases. Many cases have a late malignant phase, or become associated with Hodgkin's disease, lymphatic leucemia, or a polymorphous cell sarcoma.^{19, 20, 21}



Fig. 195.—Giant follicular lymphoblastoma of the spleen.

The lymph nodes are enlarged, firm, and discrete (until late). The spleen is usually greatly enlarged (average 1,600 Gm.). The cut surface is studded by grayish areas, 1 to 3 mm. in diameter, which represent the greatly hypertrophied Malpighian corpuscles. Microscopically, the essential change is a tremendous increase in number and size of the germinal centers of lymph follicles, which are surrounded by a narrow rim of small dark mature lymphocytes. The enlarging follicles may fuse and assume irregular shapes. Invasion of the capsule and tissues beyond occurs in late stages.

The condition is easily distinguished microscopically from the other types of lymphoblastoma by the maintenance and exaggeration of the follicular architecture. It is most easily confused with the lymphadenitis of secondary syphilis (see p. 136) and other inflammatory hyperplasias. The latter benign reaction of lymphatic tissue to infections or irritative

processes is most marked in children, whereas follicular lymphoblastoma occurs in late adult life. The histologic differences between follicular lymphoblastoma and inflammatory hyperplasia are outlined in Table X (From Baggenstoss and Heck²²).

TABLE X

HISTOLOGIC DIFFERENCES BETWEEN FOLLICULAR LYMPHOBLASTOMA
AND INFLAMMATORY HYPERPLASIA

	FOLLICULAR LYMPHOBLASTOMA	SIMPLE HYPERPLASIA OF INFLAMMATORY OR TOXIC ORIGIN
Follicles	Larger and more numerous Closely packed Diffuse throughout node Frequent in medulla Uniformly large Tend to fuse	Smaller and less numerous Scattered Arranged around cortex in concentric rows Few in medulla Vary in size Are discrete
Interfollicular tissue	Cells densely packed Condensation of reticulum Sinuses narrowed or blocked Slight proliferation of reticular cells	Cells scattered Loose reticulum Sinuses open—often dilated Marked proliferation of reticular cells

Lymphosarcoma

Lymphosarcoma is a malignant tumor which can arise from any aggregate of lymphoid tissue. It may occur at any period of life, but the average age is about 45 years. Constitutional symptoms and blood changes are lacking in early stages. External lymph node enlargement is the most frequent beginning, and the cervical nodes are most often affected. The gastrointestinal tract is frequently involved. Direct invasion and extension to contiguous lymph nodes occurs early. Later widespread extension, probably by the blood stream, often results in involvement of many tissues. The tumor tissue is highly radiosensitive.

Lymphosarcoma probably arises from the undifferentiated mesenchymal stem cell of lymphoid tissue.²³ Lymph follicles are composed of two types of cells, the small lymphocytes arranged about the periphery, and the large pale reticulum cells of the germinal center. Differentiation may be different in degree or direction, so that two types of lymphosarcoma may be distinguished, a small cell type (malignant lymphocytoma) and a large cell type (reticulum-cell sarcoma).^{24, 25} This latter term, reticulum-cell sarcoma, is re-

served by some for the most undifferentiated types of lymphosarcoma, composed of syncytial masses of cells with large, very pale nuclei.²⁸

The essential microscopic feature of lymphosarcoma is disruption and obliteration of the architecture of the lymphoid tissue by the cellular overgrowth. Pleomorphism is not a feature, most of the cells being similar in appearance, though some giant-cell forms may occur. Mitoses are present but not necessarily abundant. In lymph nodes the capsule eventually is penetrated, and there is invasion of surrounding tissue. In the intestinal tract, invasion occurs throughout the walls of the bowel. Fibrosis or granulomatous changes are lacking. Silver stains show a variable number of fine reticulin fibers.

Lymphosarcoma is closely related at one end of the scale to follicular lymphoblastoma, and at the other end to Hodgkin's sarcoma.

Hodgkin's Disease

Hodgkin's disease involves lymph nodes or lymphoid tissue elsewhere, as in the alimentary tract, spleen and, often, bone marrow.²⁹ The etiology is unknown, and its nature is a matter of debate. The most popular conceptions are that it is (1) a chronic infective granuloma, or (2) a true neoplasm of lymphoid or reticulo-endothelial origin. At least one form or stage, often termed Hodgkin's sarcoma, has the characteristics of a malignant tumor. The belief that it is an atypical form of tuberculosis has been almost abandoned. Organisms of the *Brucella* group have been cultured from cases which appeared to be Hodgkin's disease,³² but an etiologic relationship has not been established as yet.

A fatal ending occurs after an average duration of two years, but length of life varies from a few months to ten years or more. Males are affected more than twice as frequently as females. It may occur at any age, but the highest incidence is in young adults.²⁹

The beginning is usually a painless enlargement of a group of lymph nodes, most frequently in the neck. Itching is often an accompaniment. Blood changes are inconstant, but there may be a moderate polymorphonuclear leucocytosis with lymphopenia, and eosinophilia is occasionally present. Anemia develops in later stages. The disease progresses by further involvement of lymphoid tissue, as in other groups of nodes, spleen, etc. In late stages various viscera become

involved. Almost any tissue eventually may be affected, although the nervous system is seldom involved except by Hodgkin's sarcoma. Radiation, to which the tissue is moderately sensitive, is the usual method of therapy.



Fig. 196.—Hodgkin's disease of spleen. The suet-like areas of Hodgkin's tissue are seen on the cut surface. (Courtesy Dr. H. C. Schmeisser.)

The enlarged involved lymph nodes are at first discrete, but in late stages they become matted together. The cut surface of the Hodgkin's tissue has a grayish, translucent,

"fish-flesh" appearance. Diagnosis is usually made by biopsy of a lymph node. The whole of an enlarged node should be resected for such purpose. Gordon's test for Hodgkin's disease consists of the intracerebral inoculation of rabbits or guinea pigs with suspensions from involved lymph nodes. In positive cases the animal develops encephalitic signs. While this biologic test has been believed to support the infective nature of Hodgkin's disease, there is evidence that it is nonspecific and may be a reaction to eosinophiles.³⁰



Fig. 197.—Hodgkin's disease, retroperitoneal lymph nodes. (Courtesy Dr. H. C. Schmeisser.)

The histologic picture in Hodgkin's disease is that of a diffuse progressive granulomatous or neoplastic process, beginning with lymphoid hyperplasia. With progression of the lesion, there is gradual loss of normal architecture due to replacement by a pleomorphic cellular tissue in which large hyperchromatic characteristic cells (Sternberg or Dorothy Reed cells) are an essential constituent. Eosinophiles are often numerous, but they are not invariably present. In certain cases there is invasion, and the tissue

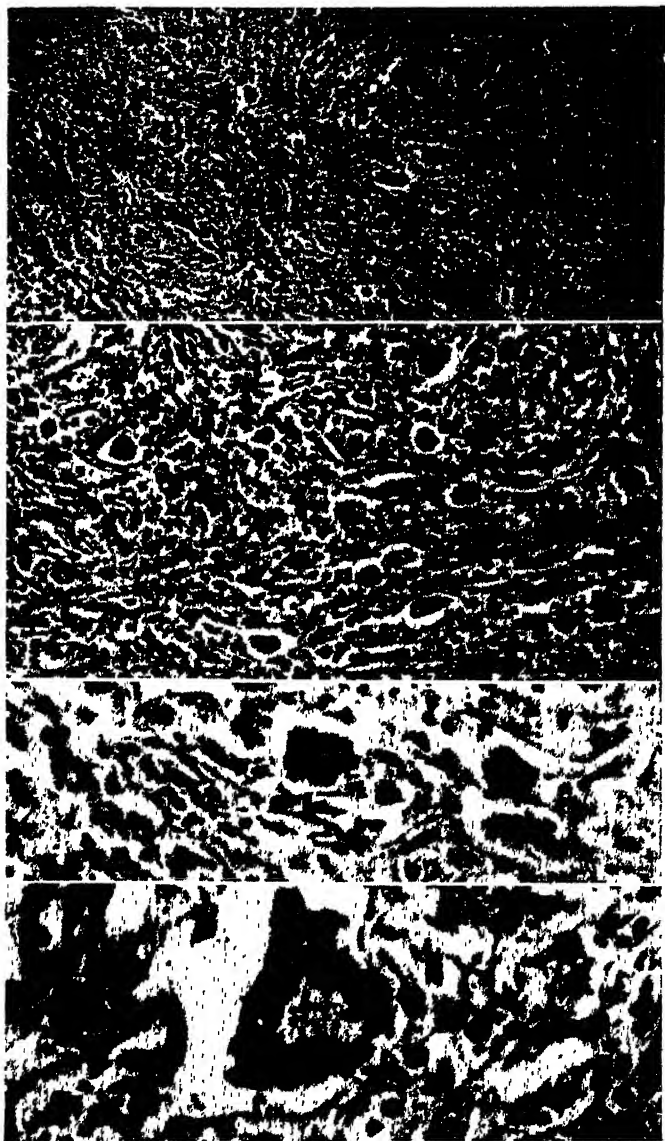


Fig. 198.—Hodgkin's disease. Note the characteristic large hyperchromatic cells which stand out prominently. Some fibrosis is evident in the upper figures.

has a sarcomatous aspect. Areas of necrosis may occur. Fibrosis with hyalinization is a late development.

The important histologic features are (1) the Sternberg or Dorothy Reed cells, (2) the pleomorphism of the cellular tissue, (3) the presence of eosinophiles, and (4) fibrosis. The Sternberg-Reed cells are large (12 to 40 microns), often irregular in shape, and with lobulated or multilobed nuclei. Multinucleated forms also occur. The nuclear chromatin is abundant and dark-staining, and nucleoli are prominent. Their hyperchromatism may cause them to stand out prominently in the first glance at a microscopic field. The cytoplasm is abundant, and may be either acidophilic or basophilic. The appearance of Reed-Sternberg cells is often similar to that of megakaryocytes. Pleomorphism is prominent in the usual case, in that there is a mixture of the specific cells, giant cells of Hodgkin's disease, plasma cells, lymphocytes, leucocytes, and eosinophiles. The occurrence of eosinophiles is important. While not invariably present in Hodgkin's disease, they rarely occur in large numbers in lymph nodes in any other condition. Fibrosis is important in distinguishing Hodgkin's disease from other lymphoblastomatous conditions such as lymphosarcoma and lymphatic leucemia.

Attempts have been made to divide Hodgkin's disease into histologic types,^{33, 34} from which an estimate of the course and prognosis sometimes can be made. The most benign form, Hodgkin's lymphoma or paraganuloma, is essentially a disease of lymph nodes, most frequently of the cervical group. There is a proliferation of lymphocytes, the predominant cell, with disturbance of the architecture of the lymph node varying from slight to severe. Variable numbers of Reed-Sternberg cells are present, on which the diagnosis is based. Pleomorphism, necrosis, and fibrosis are absent. In time this type may become transformed into Hodgkin's granuloma. Hodgkin's granuloma, the most frequent variety, is characterized by pleomorphism, Reed-Sternberg cells, eosinophiles, necrosis, and fibrosis. Widespread involvement ensues. Hodgkin's sarcoma or lymphoreticuloma has a neoplastic character and is characterized by anaplastic cells, often with frequent mitoses, lymphocytic and reticulum cell hyperplasia, and scattered typical Reed-Sternberg cells. Pleomorphism and fibrosis are not prominent features. The behavior is that of a highly malignant and invasive tumor. This type has a higher proportionate incidence in older age groups.³⁵

LIPOIDOSES

The lipoidoses (lipoid storage diseases) are a group of conditions in which an abnormal accumulation of fatty substance occurs within reticulum cells or tissue histiocytes. Often congenital or familial, they are the result of an abnormality of fat metabolism. It has been debated whether the large fat-holding cells are active participants in the disturbed metabolism or simply passively accumulate the lipoids in abnormal amount. The main types of lipoidoses and the fatty materials involved are outlined in Table XI.

TABLE XI
LIPOIDOSES

DISEASE	LIPOID SUBSTANCE	ORGANS AND TISSUES INVOLVED
Gaucher's disease	Cerebroside (kerasin)	Spleen, liver, bone marrow, skin, brain (infantile or acute neurologic form).
Niemann-Pick disease	Phospholipid (sphingomyelin and lecithin)	Generalized—reticulo-endothelial, epithelial, and connective tissue cells.
Amaurotic Family Idiocy (Tay-Sachs Disease)	Phospholipid	Central nervous system—glial and ganglion cells.
Xanthomatōses Hand-Schüller-Christian disease	Cholesterol ester	Multiple involvement of skeletal system—bone marrow of skull and femur particularly. Lung sometimes involved.
Xanthoma palpebrum	Cholesterol	Skin, particularly of upper eyelids.
Xanthoma tuberosum multiplex	Cholesterol	Skin, tendons and tendon sheaths, peri-articular tissues.

Gaucher's Disease.—Gaucher's disease (cerebroside lipoidosis) is a chronic familial disease in which the cerebroside, keraasin, accumulates in reticulum cells of the spleen, liver, lymph nodes, and bone marrow. Beginning in childhood, it extends into adult life, and the course of the disease may extend twenty years or more. The spleen increases progressively in size to reach a weight of 2,000 to 3,000 Gm. The liver and lymph nodes are enlarged to lesser degrees. Hemosiderosis, pigmentation of skin and conjunctiva, mild

anemia and leucopenia are usually present. An acute infantile form of the disease also occurs, in which neurologic manifestations are prominent.

The hypertrophied spleen is firm, reddish-brown in color, and studded with grayish-white translucent masses. The liver also is pigmented and shows discrete whitish nodules, and similar masses involve lymph nodes and bone marrow. Microscopically, the distinctive feature consists of the large, pale Gaucher cells, which compose the grayish translucent areas. These cells measure 20 to 40 microns or more in diameter, have a small eccentric nucleus, and abundant pale cytoplasm containing fine threads. Multinucleated forms occur. The intracytoplasmic lipid does not stain with the ordinary fat stains.

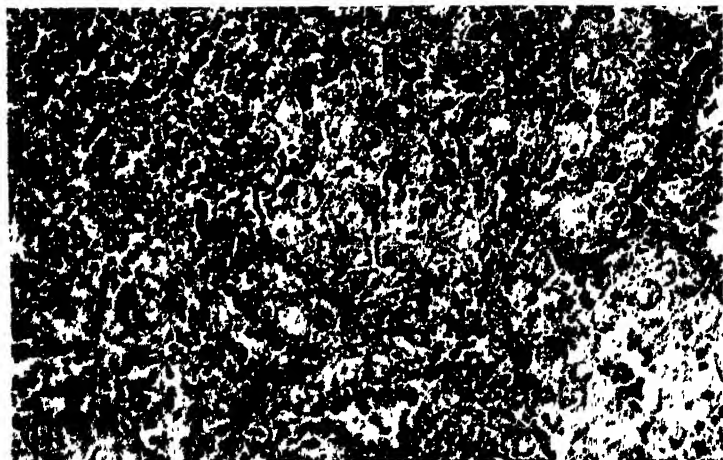


Fig. 199.—Gaucher's disease of spleen. Note the masses of large, lipid-filled cells.

Niemann-Pick Disease.—In Niemann-Pick disease (phosphatide lipoidosis, lipid histiocytosis) the phosphatides, sphingomyelin and lecithin, accumulate in cells of the reticulo-endothelial system and in histiocytes in many organs and tissues. Young infants are affected, and death usually occurs before the age of two years. The neutral fat, fatty acid, and cholesterol of the blood are increased.

The spleen, liver, lymph nodes, lungs, and bone marrow are most involved, but the lipid-containing cells may be

found in any organ. The characteristic cells are smaller than Gaucher cells and have a foamy appearance due to many fine vacuoles of lipoid in the cytoplasm. There is no hemosiderosis. The disease has a close relationship to the infantile form of amaurotic family idiocy (Tay-Sachs disease) in which a phospholipid is present in the glial and ganglion cells of the nervous system.

Xanthomatosis.—Xanthomas are localized accumulations of cells containing lipoid (mainly cholesterol). The lesions have a yellow color in the gross and microscopically are made up of large cells filled with doubly refracting lipoids. In some cases they are primary or idiopathic, and in other instances they are secondary to disturbances of fat metabolism, as in diabetes mellitus. The most common sites are in the skin or about tendons. The xanthoma cells are large, rounded, and have a vacuolated cytoplasm. Unlike the other lipidoses the cells of a xanthoma tend to break down and release their fat so that a granulomatous reaction and fibrosis may be elements in the lesion.

The *Hand-Schüller-Christian syndrome* is an osseous type of xanthomatosis, the skull particularly being affected. It may occur in childhood or adult life. There is often a characteristic triad of symptoms: defects of membranous bones, exophthalmos, and diabetes insipidus. Blood cholesterol is not increased. The defects in bones are filled by yellow granulomatous material with many xanthoma cells containing cholesterol. Similar deposits in the pituitary region cause diabetes insipidus, and in the orbit lead to exophthalmos. The lung may be involved and become diffusely fibrosed. There is not much generalized storage in the reticulo-endothelial system. It is probable that Letterer-Siwe disease and eosinophilic granuloma are variants of this disease, or related conditions.^{17, 27, 29}

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CHAPTER XVII

THE BLOOD AND BLOOD-FORMING ORGANS

The conditions in which alteration in the constituents of the blood is the prominent feature are primarily diseases of blood-forming tissue, and especially of bone marrow. The changes in the blood, which are most easily studied clinically, are reflections of the basic defect in hematopoietic structure and function. The following is a simplified classification:

I. Diseases involving red cells

1. Deficiency of red cells and hemoglobin—*anemia*
2. Excess of red cells—*polycythemia*

II. Diseases involving white cells

1. Deficiency of white cells—*leucopenia* and *agranulocytosis*
2. Excess of white cells—*leucocytosis* and *leucemia*

III. Hemorrhagic diseases

DISEASES INVOLVING RED BLOOD CELLS

Anemia

In anemia there is a quantitative deficiency of hemoglobin and usually it is accompanied by a corresponding decrease in number of red blood cells. About 14.5 Gm. of hemoglobin per 100 c.c. of blood is the normal for an adult. Different types of anemia show varying degrees of dissociation between the reduction of hemoglobin and of red cells.

GENERAL FEATURES OF ANEMIA

Although anemias of particular types have certain pathologic changes which are more or less characteristic, there are also features common to all severe anemias. These include pallor of skin, mucous membranes, fat and muscle, and fatty change in the heart and liver. In severe anemias, fatty degeneration of the myocardium is often of extreme degree, and especially prominent on the endocardial surface where thrush-breast markings may be seen (see p. 271). Atrophic changes frequently affect the mucosa of the alimentary canal. Small hemorrhages of skin, mucosal and serous surfaces are common

terminally. Red blood cells show variations in size (anisocytosis), shape (poikilocytosis), and staining properties (polychromasia).

CLASSIFICATION OF THE ANEMIAS

An etiologic classification of the anemias is, in many cases, readily correlated with morphologic and other changes in the red cells which can be determined by laboratory tests.¹ It is also helpful as a guide to rational therapy. It is recognized, however, that not all anemias are as yet readily classifiable on this basis.

I. Anemias resulting from defective blood formation, due to

1. Deficiency

A. Deficiency of iron (microcytic and hypochromic anemia)

a. chlorosis

b. idiopathic hypochromic anemia

B. Deficiency of a specific hemopoietic principle (macrocytic and hyperchromic anemia)

a. pernicious anemia

b. sprue

c. megalocytic anemias of pregnancy, etc.

2. Other factors

A. Aplastic anemia

B. Anemia of nephritis

C. Anemias due to carcinomatosis of bone, and osteosclerosis (myelophthisic anemia)

D. Anemias of thyroid deficiency (myxedema) and scurvy

E. Sickle-cell anemia

F. Erythroblastic anemias

II. Anemias due to excessive blood loss

1. Hemolytic anemias—excessive blood destruction within the circulation

A. Acute and chronic hemolytic anemia (jaundice)

a. congenital

b. acquired

2. Hemorrhagic anemias—loss of blood from acute and chronic hemorrhages

Iron-Deficiency Anemias.—When there is deficiency of iron supply, hemoglobin cannot be formed in sufficient quantity. Hence the red cells are hypochromic, or have a low concentration of hemoglobin, and tend to be of smaller size (microcytosis). Insufficient dietary intake of iron is most important in this type of anemia, but other factors such as failure of absorption or faulty metabolism of the iron may be at fault.

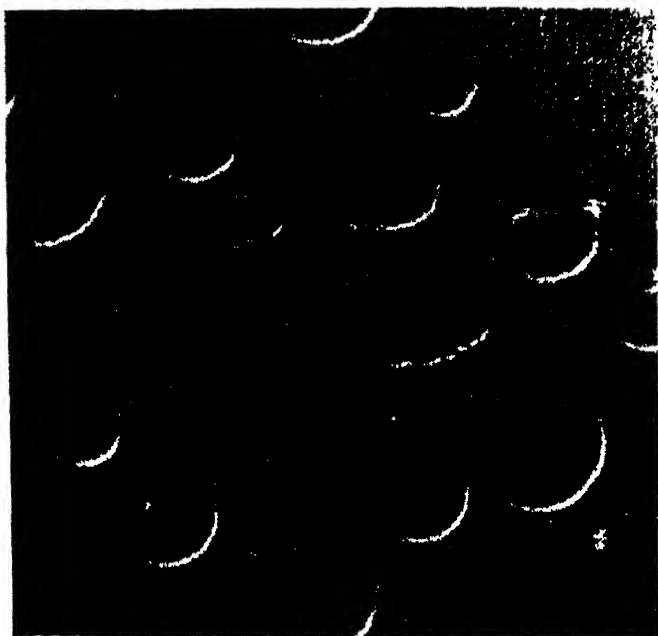


Fig. 200.—Pernicious (macrocytic) anemia, profile printing of red cells. (Courtesy of Dr. W. P. Murphy, from *Arch. Int. Med.* 71: 814, 1943.)

Chlorosis is an anemia characterized by a faintly greenish pallor of the skin, and it responds remarkably to iron therapy. Rarely encountered now, it is said formerly to have been very common among young women.

Idiopathic hypochromic anemia is frequent among middle-aged women. There may be soreness and atrophy of the mucosa of the tongue, and achlorhydria is often present.

Dysphagia is a peculiar complication of some cases (Plummer-Vinson syndrome). Iron therapy is effective.

Pernicious Anemia.—Pernicious anemia (Addison's anemia) was formerly referred to as a primary anemia. It is due to deficiency of an erythrocyte-maturing principle, formed by the combination of an extrinsic factor in the diet with an intrinsic factor supplied by gastric secretion. The liver acts as a storehouse of the maturation principle. In the absence of this substance the normal maturation of erythroblasts to normoblasts is interfered with, and large primitive red cells (megaloblasts) are formed, some of which are passed into the blood stream along with other immature forms of red cells. The average size of the circulatory red cells is large (i.e., the anemia is macrocytic) and the cells are usually well filled with hemoglobin (hyperchromic). Excessive hemolytic activity is present, as evident from an abundant hemosiderin deposit in the liver and spleen.

The highest incidence is in middle life. Severe degrees of anemia develop, but temporary remissions are common. Soreness of the tongue, achlorhydria, and gastrointestinal disturbances are usually present. Remarkable results follow liver therapy, which supplies the missing substance necessary for normal blood formation. A few cases are complicated by degenerative lesions in the dorsal and lateral columns of the spinal cord (subacute combined degeneration—see p. 703).

In fatal cases the skin and fat may be noted to have a lemon-yellow tinge. Fatty degeneration is often prominent in the heart and may be evident also in the liver and kidneys. There is excessive hemosiderin deposit in the liver and spleen. The mucosa of the stomach is atrophic, particularly in the proximal two-thirds, with disappearance of oxyntic and peptic cells and replacement of the fundic type of glands by less differentiated abnormal glands. The pyloric portion may be altered only slightly (see p. 469). Atrophic changes also affect the epithelium of the tongue.

The hematopoietic tissue of the bones is hyperplastic, and a deep red marrow is found in the long bones which normally harbor a yellow fatty marrow. The hyperactive marrow is composed almost entirely of erythroblastic tissue.

In sprue and celiac disease (steatorrhea) there is a failure of gastric digestion. Macrocytic anemia is often present, presumably due to failure of formation or absorption of the erythrocyte maturing principle. Involvement of the gastrointestinal tract in other ways is followed at times by macrocytic anemia, e.g., in carcinoma of the stomach and *Dibothrio-*

cephalus latus infection. Some of the anemias which complicate pregnancy are of a similar macrocytic type, but their origin is more obscure.

Aplastic Anemia.—In aplastic anemia there is a failure of maturation of blood-forming cells at an early undifferentiated stage. An extreme degree of anemia results, in which evidence of regenerative activity of the blood is lacking and the red cells present are of approximately normal size, shape, and staining (normocytic, normochromic).

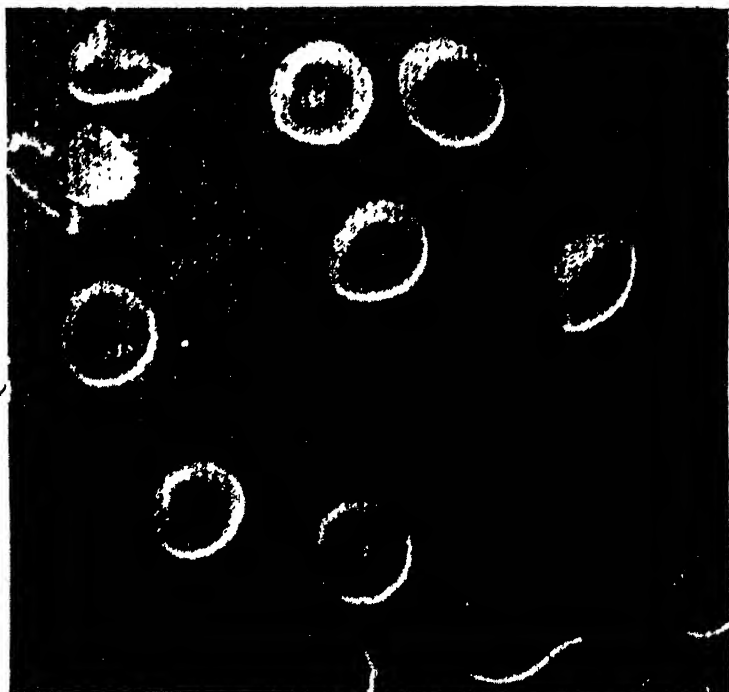


Fig. 201.—Hypochromic anemia, profile printing. (Courtesy of Dr. W. P. Murphy, from Arch. Int. Med. 71: 814, 1943.)

Leucocytes are also depressed. The condition is rapidly progressive and fatal, with hemorrhagic and purpuric phenomena prominent in late stages. The causation is usually unknown, but in some cases chemical poisons such as benzol and trinitrotoluene act as the specific marrow de-

pressant. The greatest incidence is in women during the ages of adolescence or early adult life.

The post-mortem findings are those of a severe anemia, such as fatty change of the heart and petechial hemorrhages of serous surfaces. The changes actually found in the bone marrow are variable.² The normally red marrow may be aplastic, appearing yellow and fatty. In other cases, however, the marrow is active or even hyperplastic, but it exhibits failure of maturation of the hemopoietic cells at an early stage.

Anemia of Nephritis.—A hypochromic anemia is a common accompaniment of nephritis, sepsis, and other infective conditions. It is apparently due to some toxic effect on the bone marrow and responds poorly to treatment unless the causative factor is removed.

Myelophthisic Anemia.—This type of anemia is due to replacement of the blood-forming tissue of the bone marrow. Widespread tumor growth replacing marrow tissue may act in this way, as a result of multiple myeloma (see p. 664) or metastatic carcinoma from the breast, thyroid, prostate, kidney, etc. A similar effect is observed in osteosclerotic bone disease in which overgrowth of dense bone encroaches on the marrow (see p. 648).

The anemias of myxedema and scurvy are usually hypochromic. There is evidence that adequate thyroxin and vitamin C are necessary for normal blood formation.

Sickle-Cell Anemia.—A mendelian-dominant hereditary peculiarity of red cells is found in about 8 per cent of Negroes. This peculiarity, referred to as sickle anemia or the sickle cell trait, is the tendency to assume bizarre shapes when exposed to low oxygen tension, many of the cells becoming elongated, pointed, and sickle shaped. A small proportion (1 in 40) of Negroes with the trait develop sickle-cell anemia. A greater lowering of the oxygen tension is necessary to produce sickling in sickle anemia than in sickle-cell anemia. The sickling can be observed in blood preserved in sealed moist slide preparations, or in tissues fixed in formalin or Zenker's solution. Sickled cells are found in high percentages in the venous circulation in sickle-cell anemia, but not in the peripheral circulation of individuals with sickle cell trait alone. The anemia is at least partially hemolytic in type, and there are signs of red cell destruction, as well as of increased regenerative activity on the part of the bone marrow.

Pathologic features of sickle-cell anemia³ include the sickled erythrocytes, and thrombi in small vessels, with development

of areas of infarction and fibrosis. Thrombi in cerebral vessels may lead to infarction of the brain. Hemosiderin deposits are found in the spleen, liver, bone marrow, lymph nodes, and kidney. The bone marrow is hyperplastic, its activity being evident from the regenerative blood picture.



Fig. 202.—Sickled red blood cells. Upper: In a moist preparation. Lower: In the lumen of a blood vessel.

The splenic changes in sickle-cell anemia are particularly noteworthy. In early stages the spleen is enlarged, and extreme congestion or hemorrhage is noted around the Malpighian corpuscles. Later fibrosis develops, with marked pigment de-



Fig. 203.—The spleen in sickle-cell anemia. Upper: The early stage, with a ring of hemorrhage around a Malpighian body. Lower: The late stage, with fibrosis and incrustation with pigment (siderofibrosis).

posits and the formation of siderofibrotic nodules (Gandy-Gamna bodies—see p. 417). Fibrotic atrophy of the spleen may progress to an extreme degree.^{4, 5}

Erythroblastosis Fetalis.—Erythroblastosis is a congenital disturbance of blood formation, in which immature red cells are present in the circulation in excessive number. There may be an accompanying excessive hemolysis, and extramedullary hemopoiesis (particularly in spleen and liver) is often present. Some cases have marked edema and ascites (hydrops fetalis), while intense and persistent jaundice is prominent in others (icterus gravis neonatorum). The basal ganglia of the brain may show bile pigmentation (kernicterus). Fatty change or even more severe degeneration is sometimes present in the liver.

The Rh factor has recently been suggested to have a role in the pathogenesis of erythroblastosis. About 15 per cent of individuals are said to lack the Rh factor in their blood. The child of an Rh-negative mother and an Rh-positive father tends to inherit the dominant Rh factor. In this case the fetus may cause the production of anti-Rh agglutinins in the maternal blood, which in turn penetrate the placental barrier and cause destruction of fetal red cells. Macklin⁶ has emphasized the significance of the demonstration of stored iron in the infant's liver by the Prussian blue technique, indicating excessive blood destruction, in the confirmation of Rh incompatibility.

For a similar reason, Rh-negative mothers are apt to suffer serious hemolytic reactions if transfused with Rh-positive blood.^{21, 22}

Cooley's anemia is another type of erythroblastic anemia which has a familial occurrence among Mediterranean races. The bone marrow is hyperplastic, and in the thickened skull trabeculations are prominent on x-ray examination.

Hemolytic Anemias.—The hemolytic anemias are those in which excessive destruction of red cells in the circulation is the main feature. Pernicious and sickle-cell anemias also have excessive red cell destruction but are not considered here as primarily hemolytic anemias because of their other important characters.

Hemolytic anemia (hemolytic icterus, acholuric jaundice) occurs in congenital and acquired forms. The congenital form is of familial occurrence, becomes manifest at an earlier age, and tends to be milder than the acquired form. The red cells are rounded, forming biconvex discs (spherocytes) and are excessively fragile. Their fragility is demonstrated by

their decreased resistance to hypotonic saline solutions. In such solutions laking begins at a concentration of about 0.7 per cent and is complete at 0.46 per cent (corresponding normal figures are 0.44 per cent and 0.35 per cent). The spherocytosis has been regarded as a congenital abnormality in the form of the red cells which rendered them less resistant.

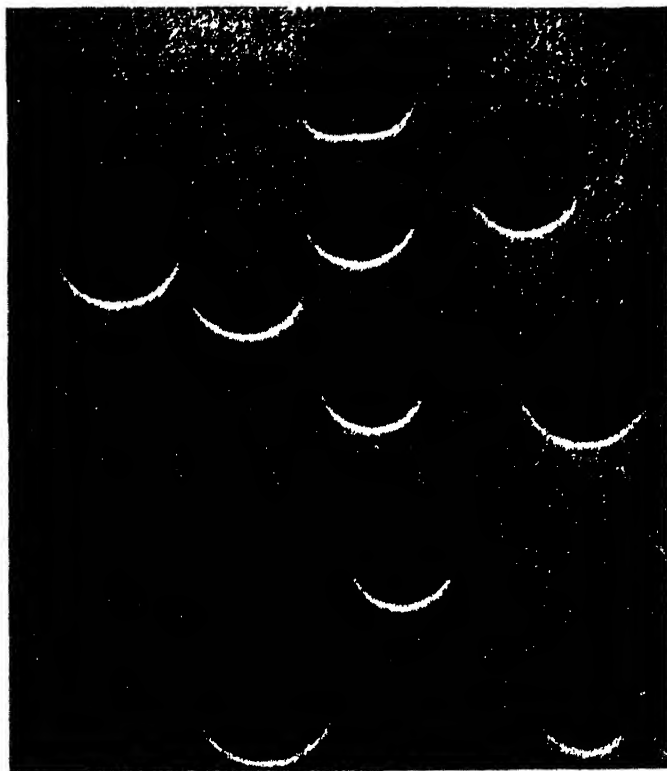


Fig. 204.—Hemolytic anemia. Profile printing of red blood cells showing spherocytosis. (Courtesy of Dr. W. P. Murphy, from *Arch. Int. Med.* 71: 814, 1943.)

Later evidence has indicated that spherocytosis (and increased fragility) may be present in acquired hemolytic anemias also, the changed form being due to the action of a lytic agent on mature red cells.⁷ Hemolysins may be demonstrable in the acquired form. Jaundice results from the excessive bilirubin production, and when the hemolytic action

is violent, there may be hemoglobinuria also. Pigment stones often form in the gall bladder. Extreme normoblastic hyperplasia of the bone marrow occurs in an attempt to replace the destroyed red cells, and numerous reticulocytes in the circulating blood reflect this regenerative activity.

The spleen shows the changes of greatest interest, being markedly enlarged, with distention and congestion of the pulp sinuses. Excess pigment deposit and even siderofibrotic nodules may be present. Histiocytic proliferation, with phagocytosis of red cells and giant-cell formation, is observed in certain cases. Multiple areas of thrombosis and infarction also may be present. Splenectomy is usually followed by prompt clinical recovery, apparently due to removal of the major mechanism of destruction of the fragile red cells. The fragility of the red cells is not corrected, however.

Anemias Due to Hemorrhage.—Loss of blood is one of the commonest causes of anemia. The loss may be acute and severe, or repeated mild hemorrhages. The anemia is hypochromic in type and may be of severe grade.

Polycythemia

Polycythemia is an increase in number of red blood cells. Counts of 7 to 10 million red cells per cubic millimeter of blood may occur. The cases can be divided into two groups: (1) a mild type, **erythrocytosis**, secondary to or compensatory for various conditions in which there is poor oxygenation, such as in congenital heart disease of certain types, pulmonary arteriosclerosis (Ayerza's disease), high altitudes, etc. (2) **Erythremia (polycythemia rubra, Vaquez-Osler disease)** in which the polycythemia is more pronounced, and of unknown etiology or not obviously secondary to a condition of poor oxygenation.

Polycythemia rubra usually appears in middle life. It is frequently considered as a neoplastic change of erythropoietic cells, comparable to a leukemia. Some evidence suggests that it may be due to local anoxemia in the bone marrow itself as a result of arteriosclerotic or inflammatory changes in skeletal vessels, with excessive erythropoiesis as misdirected overcompensation.⁸ The increase of red cells is due to overproduction, rather than to any greater longevity or decreased destruction of the cells.

The main pathologic finding is engorgement and hyperplasia of bone marrow. The liver and spleen are enlarged and hyperemic. Engorgement of vessels is widespread; hemorrhages and thromboses are common.

DISEASES INVOLVING WHITE BLOOD CELLS

Agranulocytosis

Agranulocytosis is a depression of leucocyte formation, with an extreme decrease in the number of white cells in the blood. It is frequently associated with severe infection, and necrosing ulceration of the mucosa of the mouth and pharynx (agranulocytic angina). Absence of severe anemia distinguishes agranulocytosis from aplastic anemia, and absence of thrombocytopenia distinguishes it from aleucemia. Most cases are caused by hypersensitivity to the toxic effects of certain drugs, amidopyrine being the most frequent and serious offender. Other cases are caused by dinitrophenol, arspenamine, thiouracil, and sulfonamides. The findings in the bone marrow are variable. While usually aplastic, in some cases the marrow appears normal or even hyperplastic.

Primary Splenic Neutropenia.—A condition in which there appears to be excessive destruction of neutrophilic leucocytes by the spleen has been termed primary splenic neutropenia.^{9, 10} In addition to the decrease of granular leucocytes in the peripheral blood, there is splenomegaly and myeloid hyperplasia of the bone marrow. Splenectomy is curative. Examination of the spleen shows many neutrophiles being phagocytized by macrophages.

Leucemia

Leucemia is a condition of lawless overgrowth of white blood cells and proceeds to a fatal ending. It is probably best regarded as a neoplastic change in blood-forming tissue, in most cases accompanied by flooding of the blood and tissues with the excess of white cells, many of which are immature or abnormal forms. Those unusual cases in which excessive or abnormal white cells are not found in the blood are referred to as aleucemic leucemia. The aleucemic condition may be but a transient phase in the course of the disease, but in rare cases is present from beginning to end.

The bone marrow, considered as a blood-forming organ, is large and labile in activity, in the adult comprising about 1,400 c.c., almost the size of the liver. Only a small proportion of this organ, represented by red marrow, normally is active in blood production. The remaining latent yellow or fatty marrow is replaced by active red marrow when there is greater demand for blood cells. In leucemias the entire

marrow may be activated into grayish red, densely cellular, leucocyte-forming tissue. Crowding out of erythroblastic tissue results in anemia. Two substances have been extracted from the urine of patients with leucemia, one of which stimulates proliferation (but not maturation) of myeloid cells, and the other promotes proliferation of lymphoid cells without maturation.¹⁵

According to the type of white cell involved, the leucemias are classed as myeloid, lymphatic, and monocytic. Each of these may be acute or chronic, but the acute types are difficult to distinguish from each other. There is a different age incidence for the various types. Acute leucemia has its maximum incidence in the first decade, chronic myeloid leucemia between 25 and 45 years, and chronic lymphoid leucemia between 45 and 60 years. The monocytic type tends to occur more frequently in middle or older age periods.

Acute Leucemia.—Acute leucemia may begin suddenly and runs a rapid course of a few weeks or months. Early stages may be aleucemic, but later the white blood count becomes very high, though less than the extreme figures of chronic leucemia. Anemia and thrombocytopenia are often severe. The majority of white cells in the blood are myeloblasts or lymphoblasts, distinction between these primitive cells being difficult and unreliable. At autopsy the bone marrow is everywhere hyperplastic and packed with the same primitive white cells. The spleen, lymph nodes, and tonsils are usually moderately enlarged, and their sinuses are filled by the leucemic cells. The same cells may be found infiltrating the liver, heart, kidneys, and other viscera.

Chronic Myeloid Leucemia.—In the myelogenous type of leucemia there is a great increase in granular leucocytes in the blood, and many immature cells (myelocytes and myeloblasts) are recognizable in blood smears. The total white count may become very high, reaching 500,000 or more per cubic millimeter in some cases. Platelets also may be increased, but red cells progressively diminish in number. The course of the disease may extend over several years before the inevitably fatal end.

The essential lesion is a myeloid hyperplasia throughout the bone marrow, including the marrow of long bones which normally is yellow and fatty. The marrow tissue is grayish brown and fairly firm. Myelocytes are predominant micro-

scopically, but granular leucocytes in all stages of development are present. The spleen becomes enormously enlarged, dark red, and firm. Masses of myeloid cells replace the lymphoid tissues and obscure the usual splenic architecture.



Fig. 205.—Mesenteric lymph nodes, chronic lymphatic leucemia. (Courtesy Dr. H. O. Schmeisser.)

The liver is also considerably enlarged and is infiltrated by myeloid cells. Similar but milder myeloid infiltration is found in the kidneys, heart, and other viscera. The un-

usual numbers of leucocytes in the lumina of blood vessels may be noted in any organ or tissue. Lymph nodes are but slightly enlarged.

Chronic Lymphatic Leucemia.—The white count is lower in lymphatic leucemia than in the myeloid type. It is usually below 100,000, and often 90 per cent or more are lymphoid cells. Red cell reduction and anemia occur in late stages, but to a lesser degree than in myeloid leucemia.

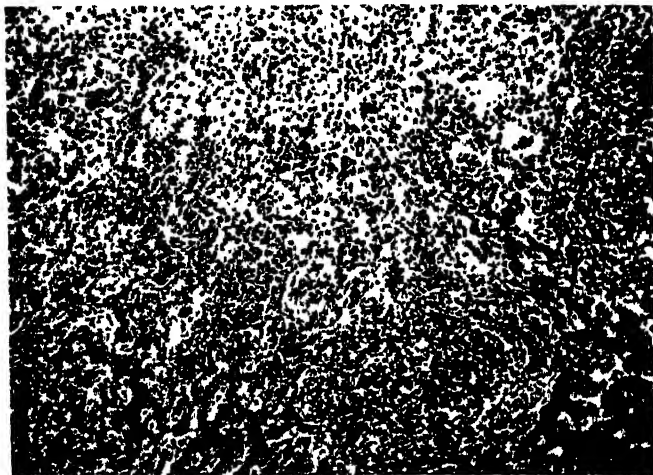


Fig. 206.—Leucemic infiltration of the liver.

The lymph nodes all over the body are enlarged, and their normal microscopic architecture is replaced by a diffuse mass of lymphoid cells. Other lymphoid tissue as in the tonsils, thymus, intestine, etc., is similarly affected. The spleen is moderately enlarged by lymphoid hyperplasia, but not to the extreme degree characteristic of myeloid leucemia. Lymphoid accumulation is found also in the liver, kidneys, skin, etc. The bone marrow is hyperplastic throughout, firm, grayish red, and similar grossly to the marrow of myeloid leucemia. Except in early stages, the hyperplastic marrow is composed largely of lymphoid cells.

Monocytic Leucemia.—The leucemias in which mature and immature monocytes are prominent in the blood are referred to as monocytic. Two varieties are often included. The Naegeli type is characterized by immature cells intermediate between myeloblasts and monocytes and

is probably a variety of myeloid leucemia. In the **Schilling type** the immature cells resemble monocytes and reticulo-endothelial cells. In this latter variety there is hyperplasia throughout the reticulo-endothelial system, and to such cases the term **leucemic reticulo-endotheliosis** has been applied (see page 420).

Monocytic leucemia tends to run a rather acute course, often with swelling and hemorrhages of the oral mucosa. Skin lesions are more frequent than in the other types of leucemia.

Leucosarcoma.—A localized tumor composed of either lymphocytic or myelogenous cells, with the development of a leucemic blood picture, is referred to as a leucosarcoma.

Chloroma.—Rare cases of myeloid leucemia, of rather acute type and in children or young adults, have associated tumor masses of a pale greenish color referred to as chloroma. The greenish color fades rapidly on exposure to air. The tumor masses are found in close relationship to the periosteum of the bones of the face, ribs, sternum, or vertebra, and less commonly in viscera. Microscopically, chloroma is composed of myeloblastic cells.

HEMORRHAGIC DISEASES

The classical theory of blood coagulation may be expressed as two equations:

$$\begin{aligned}\text{prothrombin} + \text{thromboplastic} + \text{calcium} &= \text{thrombin} \\ \text{fibrinogen} + \text{thrombin} &= \text{fibrin}\end{aligned}$$

This clotting mechanism may be disturbed by (1) diminished prothrombin, (2) delayed liberation of thromboplastin, (3) absence of fibrinogen, and (4) the presence of anti-thrombin (heparin) in the blood. The following classification of hemorrhagic diseases, based on the above mechanism, is a modification of that proposed by Quick.^{17, 19}

I. Diminished prothrombin, due to

A. Lack of vitamin K

1. dietary origin—hemorrhagic disease of the newborn
2. faulty absorption—lack of bile salts
 - obstructive jaundice
 - biliary fistula
 - sprue

B. Liver damage—faulty utilization of vitamin K

- acute yellow atrophy
- chloroform poisoning

- II. Deficiency of thromboplastin
 - A. Diminished number of platelets
 - thrombocytopenic purpura (vascular dysfunction predominates)
 - B. Increased resistance of platelets
 - hemophilia
- III. Decreased fibrinogen
 - A. Acquired
 - 1. nutritional deficiencies
 - 2. diseases of blood-forming organs
 - 3. severe liver damage
 - 4. snake bites (certain types)
 - B. congenital
- IV. Anticoagulants in the blood
 - A. liberation of heparin into the blood
 - 1. anaphylactic shock
 - 2. peptone shock

Purpura

Purpura is the condition of petechial and ecchymotic hemorrhages in the skin and mucous membranes. Symptomatic purpura occurs in various conditions, such as leukemia, severe anemia, severe infections such as smallpox, streptococcal septicemia, etc. One type of purpura, however, appears to be a disease entity. It is associated with a decrease in the number of blood platelets (thrombocytopenia).

Thrombocytopenic Purpura.—Thrombocytopenic purpura (purpura hemorrhagica, Werlhof's disease) has not only a deficiency of platelets, but also some weakness or dysfunction of the walls of small blood vessels. Spontaneous hemorrhages occur into skin, mucous membranes, joints, and intestinal tract. It occurs chiefly in children and young adults.

The bone marrow is of normal appearance and contains a normal proportion of megakaryocytes. It has been suggested that the platelet deficiency is due to thrombocytolysis rather than to deficient formation.¹⁸ Megakaryocytes may be found in the sinuses of the spleen and liver. The spleen also shows enlarged and hyperactive germinal centers.

Hemophilia

Hemophilia is an inherited abnormality of the blood, transmitted as a sex-linked recessive mendelian factor, and

appearing only in males. The coagulation time of the blood is prolonged, but the bleeding time, clot retraction, prothrombin concentration, and tourniquet test are normal.¹⁹ Severe and prolonged hemorrhages follow trivial injuries.

It has been suggested that there is some qualitative abnormality of the platelets, which are excessively resistant and hence fail to release thromboplastin.

Favism

Favism is a sudden hemolytic attack, followed by hemoglobinuria and jaundice, due to ingestion of the seeds or inhalation of materials from the flowers of *Vicia faba* (broad bean).²⁰

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CHAPTER XVIII

THE MOUTH, THROAT, AND NECK

The skin of the face and neck is subject to most of the diseases which involve skin elsewhere (see Chap. XXIII). The face is a common site for carcinoma. Carcinomas of the upper half of the face are usually of basal cell type, whereas squamous carcinoma is more apt to be found on the lower part of the face. The face and neck are common sites for malignant melanoma, often as a transformation of a benign nevus due to irritation from shaving or rubbing by a collar.

Mouth

Congenital Malformations.—The most important developmental abnormalities are cleft lip (harelip) and cleft palate. Clefts occur at places where embryonic processes which should join have failed to unite during embryonic development. In harelip there is failure of fusion of the processus globularis and the maxillary process on one or both sides, the cleft being slightly to one side of the midline. Cleft palate may be present with or without associated harelip. Hereditary influence is important.

Inflammations.—Inflammation in the mouth (stomatitis) may be a local condition or part of a generalized disease. In scarlet fever one sees hyperemia and reddening of the mucosa of the mouth and tongue. In measles, Koplik's spots are an early sign. They are small yellowish spots on a red background seen on the mucosal surface of the cheeks in the upper molar region. Mercurial or arsenical compounds may cause ulcerative stomatitis. Vincent's organisms, a spirochete and fusiform bacillus, cause ulcerative and membranous inflammations of the gums as well as in the tonsillar and pharyngeal regions. Severe ulcerative inflammations of the mouth or pharynx often complicate agranulocytosis. In leucemias, infiltration of the gingiva is common, with hemorrhage and ulceration. Debilitated infants and children particularly are subject to thrush, a local membranous lesion of the mouth due to *Monilia albicans*. Noma is a progressive gangrenous ulcerative condition, which may lead to perforation of the cheeks.

In leucoplakia of the mouth there are irregular whitish areas on the mucosa of the lips, cheeks, tongue, or elsewhere.

The squamous epithelium has been thickened and keratinized, there is acanthosis or thickening of the prickle cell layer, and subepithelial layers contain chronic inflammatory cells. In some cases leucoplakia precedes the development of squamous carcinoma.

Syphilis may be represented by lesions of the lips or mouth in either primary or secondary stages (see p. 133). Tuberculous lesions of the mouth are uncommon.

Tumors.—Cancer of the mouth is in most cases squamous carcinoma. It may arise from the lip or any area of the oral mucosa, but in more than half of the intraoral cases it involves the tongue.

CARCINOMA OF THE LIP.—Cancer of the lip is common, particularly in males. About 95 per cent occur on the lower lip, at the mucocutaneous junction, and almost all are of the squamous cell type. The infrequent carcinomas of the upper lip are more often of basal cell type and show no marked difference in sexual incidence. Trauma and chronic irritation due to jagged or carious teeth, pipe smoking, etc., are believed to be contributing causes. Lesions such as keratoses, leucoplakia, and chronic fissures may precede the development of actual cancer. The greatest incidence is in the fifth and sixth decades of life.^{1, 3}

The early cancer may be a small nodule, warty excrescence, or chronic fissure. It develops into a painless ulcer which grows slowly. It is to be distinguished from a syphilitic chancre of the lip, which is less well defined and shows evidence of inflammation. Biopsy and microscopic diagnosis are essential in most cases. Grading according to Broders'² method (see p. 204) is helpful in prognosis and treatment.

Metastasis occurs to lymph nodes of the submental and submaxillary groups, and from there to the jugular chain of lymph nodes. More distant metastasis is rare. Extension to lymph nodes occurs earlier in the forms with microscopic evidence of high malignancy.

CARCINOMA OF THE TONGUE.—Cancer of the tongue is more common in men and has its greatest incidence in the fifth and sixth decades. Its most frequent site is the edge of the tongue in the middle third. Chronic irritations and leucoplakia may be contributing etiologic factors, as in other cancers of the mouth. The most usual form is a small ulcer or fissure, but papillary or fungating lesions also occur. The tumors are squamous carcinomas of varying grades of differentiation. Metastasis occurs most frequently to upper

deep cervical lymph nodes adjacent to the bifurcation of the common carotid artery. Extension to other groups of nodes and metastasis to other tissues tend to be more widespread than in carcinoma of the lip.⁴

EPULIS.—The term epulis is rather loosely used to indicate any benign connective tissue tumor of the gums. There are two main histologic forms, (1) giant-cell epulis, in which giant cells and blood vessels are prominent, and (2) fibromatous epulis, in which connective tissue is predominant. The giant cell form is similar histologically to the benign giant-cell tumors found elsewhere (see p. 662). The variable histologic form may simply represent stages in the development of an epulis. Epulis is often preceded by local mechanical injury to the place of origin or may grow in the socket of an extracted tooth. The tumors are benign and do not metastasize, but they may recur if incompletely removed.⁵



Fig. 207.—Epulis of gum. (Courtesy Dr. H. C. Schmeisser.)

Tumors of the Jaws

The various tumors which occur in other bones may also be found in the bones of the jaws (see p. 659). In addition a group of tumors arise from epithelial or mesoblastic tissues of developing teeth. A simple classification of these includes (1) dentigerous cysts, (2) odontomas, and (3) ameloblastomas (adamantinomas).

Dentigerous cysts are benign cystic structures in the jaws, lined by epithelium, and containing one or more imperfectly developed teeth. Bauer⁶ has demonstrated that trauma may be important in development of a cyst about an unerupted tooth. Radicular cysts, formed by chronic inflammation at the opening of the pulp canal, are lined by a

squamous epithelium derived from epithelial rests of Malassez in the periodontal membrane.

Odontomas are the result of disturbances of tooth development that may lead to an atypical growth of enamel, dentine, cementum, or of all three hard substances. Odontomas grow slowly and are surrounded by a capsule. The rare soft odontoma is formed either from the dentinal papilla or periodontal membrane.



Fig. 208.—Adamantinoma of jaw. (Courtesy Dr. H. C. Schmeisser.)

Ameloblastomas (adamantinomas) are epithelial tumors arising from cells with a potentiality for forming the enamel organ. Their histologic structure resembles certain developmental stages of the enamel organ. They are composed of irregular masses of epithelial cells divided by a connective tissue stroma. The epithelial masses are outlined by a palisade of dark-staining columnar epithelial cells. In rare instances some keratinization occurs. Cyst formation is common within the epithelial masses, so that solid, cystic, and combined forms occur.⁷

The tumor is most common in the mandible and usually appears before the age of 35. While ordinarily it does not metastasize, irregular local extension occurs, and the tumor



Fig. 209.—Adamantinoma of jaw. (Microscopic section of tumor in Fig. 208.) (Courtesy Dr. H. C. Schmeisser.)

will recur unless removal is complete. A few malignant forms with metastasis have been reported.⁸

Adamantinomas, histologically identical with those of the mandible, arise in the pituitary region (craniopharyngioma, see p. 521) and in the tibia.

Pharynx

Inflammations.—Pharyngitis is commonly due to streptococcal infection, though diphtheria and Vincent's organisms also cause characteristic pharyngeal inflammations. The tonsils are most frequently involved and are swollen and reddened, with exudate on the surface and in tonsillar crypts. When the crypts are prominently distended with pus, it is often termed "follicular tonsillitis." Epidemic tonsillitis is sometimes a milk-borne streptococcal infection. **Quinsy** is a peritonsillar abscess which may complicate acute tonsillitis. **Ludwig's angina** is a diffuse cellulitis or spread of the infection to involve structures of the neck.

Tumors.—Highly malignant tumors occur in the pharynx, arising most commonly from the posterior wall of the nasopharynx or from the tonsil. They are characterized by an earlier age incidence than malignancies in general, by predominance in the male and by a tendency to early metastasis to the lymph nodes of the neck, to the orbit, or to the cranial cavity. Metastasis may appear before the primary growth is noted. As a group, they are highly radiosensitive tumors. This factor, plus their surgical inaccessibility, makes radiation the usual form of treatment.⁹

Most of these tumors can be classified as (1) squamous-cell carcinoma, (2) transitional cell carcinoma, (3) lympho-epithelioma, and (4) lymphosarcoma.

Squamous-cell carcinoma forms a coarsely granular elevated tumor with an indurated border and ulcerated surface. Its histologic appearance is similar to that of squamous carcinoma elsewhere, with evidence of keratinization.

Transitional cell carcinoma is an epidermoid cancer in which keratinization is absent. It forms a smaller, flatter lesion than does the squamous type, with a finely granular surface. Histologically, the tumor is composed of small uniform cells having large hyperchromatic nuclei and scanty cytoplasm. The cells are more undifferentiated than those of the squamous variety.

Lympho-epithelioma, described by Regaud and Schmincke, is a tumor in which wide sheets and cords of undifferentiated malignant epithelial cells are intimately associated with

lymphoid tissue or infiltrated with lymphocytes. Many feel that this is not a distinct type of tumor, but that its representatives are more properly classified as transitional cell carcinomas and reticulum cell sarcomas.¹⁰

Lymphosarcoma may occur in a localized form or as part of a generalized lymphomatosis.

Nasopharyngeal fibroma is an uncommon tumor developing mainly in boys at or near the age of puberty, and tending to undergo spontaneous regression by about 25 years of age. It appears to arise from periosteum of bone of the vault or posterior wall of the nasopharynx. The hard tumor is composed of dense but highly vascular connective tissue.¹¹

Salivary Glands

Disturbances of the salivary glands include inflammations of the parotid, duct obstruction (usually due to calculi), and tumors.



Fig. 210.—Mixed tumor of parotid gland.

Inflammation.—**Acute parotitis** occurs in the epidemic virus disease mumps (see p. 125), and, due to staphylococcal infection, is an occasional complication following surgical operations.

Mikulicz's syndrome is a bilateral enlargement of the parotid glands, sometimes with involvement of other salivary glands and lacrimal glands. It may be of inflam-

matory origin (tuberculosis, sarcoid, etc.), or be due to leucemic infiltration or to Hodgkin's disease.

Ranula is a cyst in the floor of the mouth, from a sublingual gland or the submaxillary duct.

Uveoparotid fever (Heerfordt's syndrome) is a granulomatous involvement of the parotid glands and uveal tract (iris, ciliary body). It appears to be a form of sarcoidosis (see p. 640).

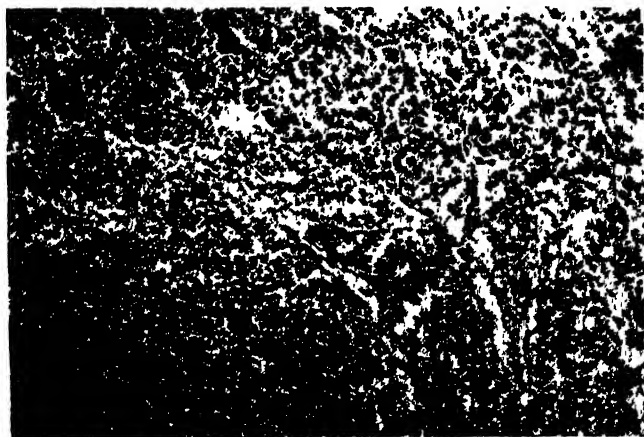


Fig. 211.—Carotid body tumor.

Salivary Gland Tumors.—A variety of tumors, including true adenomas and oncocytomas, occur in the salivary glands, but the only common type is the **mixed tumor**. This usually involves a parotid gland, less commonly a submaxillary gland or other oral site, and only rarely the sublingual glands. It may develop at any age, the highest incidence being in early adult life. The origin is uncertain. Currently popular are theories that it arises from (1) embryologically misplaced tissue, (2) branchial cleft tissue, and (3) salivary gland epithelium.^{12, 13}

Most of the mixed tumors are benign, but irregular local extension may occur through their capsule. Complete removal is often difficult and recurrence is a common event. If malignant change and metastases develop, it is usually only one element of the mixed tumor which forms the secondary growths. Lungs, pleura, liver, lymph nodes, and

bones are the common sites of metastasis. One of the serious complications of removal of the parotid tumor is injury to the facial nerve.

Mixed tumors are small, round or oval, encapsulated nodules in the parotid region. They often grow very slowly and may be present for years with few symptoms. Their consistency is rubbery, and the tumor is movable until the capsule has been invaded.

The histologic picture is complex and variable. Neoplastic cells in these tumors may be secreting epithelial cells, or myo-epithelial ("basket") cells, or both. Both types of cells are normally found in salivary glands.¹³ There are usually irregular masses or anastomosing strands of epithelial cells surrounded by connective tissue. The connective tissue portion is often myxomatous in appearance, but may be fibrous or cellular. Myxomatous transformation of the epithelial elements has been described. Areas of true cartilage or bone formed by metaplasia, and "pseudocartilag," a myxomatous degeneration of the stroma due to secretion of epithelial tumors cells, are common.

Carcinoma of salivary gland origin is most frequently an adenocarcinoma. It spreads by local invasion, and by metastasis to local lymph nodes and distal organs.

Papillary cystadenoma lymphomatosum is a benign, encapsulated cystic tumor occurring in or attached to the parotid gland. Microscopically, it is composed of papillary, tubular, or cystic epithelial structures set in a lymphoid stroma. Although the origin is debatable, most evidence suggests that it is from heterotopic salivary gland tissue in lymph nodes.^{16, 17}

Carotid Body Tumors

The rare tumors of the carotid body are found at the upper end of the common carotid artery in close relationship to the point of bifurcation. They are slowly growing tumors, which remain encapsulated until a late stage, but are potentially malignant.¹⁸ The carotid bodies being part of the chromaffin system, the tumors are chromaffinomas or paragangliomas, rather similar to the corresponding tumor of the adrenal medulla. Microscopically, they are composed of groups of epithelial cells with poorly defined boundaries, closely associated with a vascular fibrous stroma. Some of the tumors are more sarcomatous in appearance.¹⁹

Cysts of the Neck

Cysts of the neck, arising from vestigial rests, may be of thyroglossal duct origin (midline) or branchiogenic origin (lateral). The thyroglossal cysts occur anywhere between the base of the tongue and the thyroid. They are smooth-walled cysts, lined by columnar or flattened epithelium. Branchial cleft cysts most frequently appear near the angle of the jaw. The cyst lining is squamous epithelium, and lymphoid tissue is abundant in the wall. Cystic hygroma is a lymphangiomatous cyst of the neck, usually of congenital origin (see p. 243 and Fig. 92).

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CHAPTER XIX

THE GASTROINTESTINAL TRACT

Though divided into the anatomic regions of esophagus, stomach, duodenum, small and large bowel, etc., all portions of the alimentary canal consist of a hollow tube lined by secretory mucosa and with a muscular wall having peristaltic or sphincteric actions controlled by nervous influences. The same types of disease processes occur in each and follow the same general rules, but vary in their relative frequency and importance in the different portions. These types are: (1) congenital malformations; (2) diverticula; (3) inflammations and ulcerations; (4) obstructions of the lumen, acute and chronic, and (5) tumors. Table XII outlines the main lesions of the alimentary canal.

ESOPHAGUS

Congenital atresia of the esophagus is the only developmental abnormality which is common. In most cases there is an associated tracheo-esophageal fistula.

Diverticula may be of the **pulsion** type, pressure within the esophagus forcing the wall outward at a weak point, or may be due to **traction** caused by inflammatory adhesions to surrounding structures. The **pulsion** type is more common and usually involves the posterior wall at the upper end of the esophagus. The **traction** type is usually anterior and at about the level of the tracheal bifurcation. Adhesions to tuberculous mediastinal lymph nodes are the usual initiating factor.

Stenosis of the esophagus may be caused by the swallowing of corrosive chemicals, such as lye. The resulting dense fibrous tissue repair causes such stricture of the lumen as to make impossible the swallowing of solids, and eventually even liquids. Tumors of the esophagus also obstruct the lumen and give rise to dysphagia. Pressure on the esophagus from without, as by a mediastinal or pulmonary tumor, enlarged lymph nodes, or aortic aneurysm, produces variable degrees of esophageal obstruction.

Cardiospasm or functional stricture of the lower end of the esophagus is due to spasm of the cardiac sphincter. It appears to result from neurogenic imbalance of sphincteric

TABLE
 LESIONS OF THE

	ESOPHAGUS	STOMACH	DUODENUM
Congenital malformations	Atresia	Pyloric stenosis due to hypertrophy and spasm of muscle of pylorus	Rare
Diverticula	<i>Pulsion</i> type—pressure from within bulging at weak point. At upper end. <i>Traction</i> type—due to pull of inflammatory adhesions. Usually at level of tracheal bifurcation	Uncommon	Fairly common
Inflammations and ulcerations	Relatively unimportant. Follows swallowing of corrosive chemicals. Varices at lower end in obstructions of the portal circulation (cirrhosis of liver)	Gastritis results from various poisons and irritants. Chronic peptic ulcer is very frequent and important	Chronic ulcer (peptic) very common in first portion. Acute ulceration may accompany severe burns
Obstructions	1. Congenital 2. Fibrosis following ingestion of corrosives 3. Tumors 4. Cardiospasm and functional strictures of lower end 5. Pressure from without	Usually at pylorus May be (a) Congenital (infancy) (b) Scar of healed ulcer (c) Carcinoma Bezoars or concretions (masses of indigestible material)	Uncommon, except at pylorus
Tumors	Benign—uncommon Carcinoma—prognosis almost hopeless a) Squamous cell type—common b) Adenocarcinoma—rare, occurs at lower end	Benign—rare Malignant—carcinoma is very common and important Types are: a) Polypoid b) Ulcerating c) Scirrhus or infiltrating Sarcoma—rare	Rare

SMALL INTESTINE	APPENDIX	COLON	RECTUM AND ANUS
Uncommon, except for abnormalities of mesenteric attachment and rotation, and Meckel's diverticulum	Rare	Congenital dilatation (megacolon—Hirschsprung's disease)	Atresia
Meckel's—persistence of omphalomesenteric duct; 1-3 feet proximal to ileocecal junction; other types uncommon	In rare cases may follow appendicitis	Common in descending and sigmoid regions—often become inflamed (diverticulitis)	Uncommon
Typhoid—ulcerations of lymphoid areas of ileum. Regional ileitis—a chronic inflammation of terminal ileum. Tuberculosis—chronic ulcerations of lower ileum. Chemical poisons and uremia—may cause ulcerations of ileum. Lesions of jejunum are rare	Acute appendicitis is common. Complicated by perforation, abscess formation, peritonitis, pyelophlebitis	Dysentery—bacillary Dysentery—amebic Chronic ulcerative colitis Cholera Tuberculosis—may involve cecal region Actinomycosis—in cecal region	Nonspecific chronic inflammation with sinus or fistula formation is common
1. Paralytic—e.g., in mesenteric thrombosis 2. Mechanical—blockage of lumen 3. Strangulation—obstruction and interference with blood supply Biochemical disturbance with dehydration and electrolyte loss results	Commonly due to a fecolith or to fibrosis. Important in the pathogenesis of appendicitis	Acute obstruction as in small bowel. Chronic obstructions from tumors and inflammatory fibrosis	Acute obstruction is uncommon. Chronic obstruction from tumors, impacted feces, and in lymphogranuloma venereum (females)
Rare Carcinoids similar to those of the appendix occur but more rarely	Carcinoids—a benign, yellow argentaffine tumor, which histologically may resemble carcinoma. True carcinoma is rare	Benign—Polyps and adenoma are common, and prone to become malignant Carcinoma—common—particularly in distal portions of colon and rectum. Gross types are: (1) annular constricting and ulcerating and (2) papillary Histologic varieties are: (1) adenocarcinoma, (2) mucoid, (3) scirrhous	

action. As in other types of obstruction, the esophagus above the stricture becomes dilated.

Varices at the lower end of the esophagus occur in cirrhosis of the liver, due to obstruction of the portal circulation.

Carcinoma is the only type of tumor common in the esophagus. It is more frequent after the age of 50 years and more than 80 per cent occur in men. The three common sites are: (1) in the middle third of the esophagus, at the level of the tracheal bifurcation (50 per cent); (2) in the lower third, about the level of the diaphragm (25 per cent), and (3) in the upper third, about the level of the cricoid cartilage.



Fig. 212.—Carcinoma of esophagus. (Courtesy Dr. H. C. Schmeisser.)

The gross types are: (1) an infiltrating or scirrhus form which grows around the esophagus and soon produces stenosis and obstruction of the lumen; (2) a medullary type of soft, bulky ulcerating tumor; and (3) a polypoid form, which is least common.

These tumors are **squamous-cell carcinomas** of varying degree of differentiation. In rare instances an **adenocarcinoma** may be present at the lower end of the esophagus. It may arise from ectopic gastric mucosa, or be an upward extension of an adenocarcinoma of the cardiac end of the stomach.

Metastasis is more widespread in the highly undifferentiated tumors, the liver, lungs, and lymph nodes draining the area being most frequently involved. The outlook in carcinoma of the esophagus is usually hopeless, due to surgical inaccessibility, though radiologic treatment may result in palliation.

STOMACH AND DUODENUM

Congenital Pyloric Stenosis

Great hypertrophy of the circular muscle fibers of the pylorus is characteristic of this condition. Usually accompanied by spasm, it produces stenosis and obstruction of the pyloric orifice. Symptoms begin shortly after the first week of life, with vomiting, visible gastric peristalsis, and often a palpable hardened pylorus. Symptoms may subside in a few weeks, or continue for months. Recovery results after surgically splitting the circular muscle fibers of the pylorus. Though congenital, the pathogenesis of the condition is unknown, and the relative importance of spasm and muscular hypertrophy in the production of symptoms is a debatable point. The condition occurs predominantly in males. Duodenal obstruction in infancy also may be due to an **annular pancreas**, a malformation in which a band of pancreatic tissue is wrapped around the duodenum.

Syphilis of the Stomach

Syphilitic involvement of the stomach seems established as a clinical and pathologic entity, though the infrequency with which spirochetes have been demonstrated in the lesions leaves some room for doubt.

Clinically the condition simulates carcinoma. Radiologically, a smooth tube-like or funnel deformity is suggestive of syphilis. In late stages the stomach may be of the leather-bottle (*linitis plastica*) type, grossly indistinguishable from the more common scirrhus carcinoma. The age incidence in the middle thirties is lower than in carcinoma. The symptoms are of short duration in comparison with those of peptic ulcer. Free hydrochloric acid is low or absent. The Wassermann reaction is usually positive.

The lesion is a **granulomatous inflammation** which primarily involves an area of the submucosa and then often extends widely in the submucosa and muscularis. Shallow secondary mucosal ulceration may be present. The pyloric region or midstomach may be involved first, spreading to the whole stomach in late stages. The entire wall is diffusely infiltrated by lymphocytes and plasma cells, but most marked involvement is in the submucosa. There is perivascular infiltration of the inflammatory cells, and also small gummatous areas occur. Inflammatory involvement of small blood vessels, both arteries and veins, is a prominent feature. Williams and Kimmelstiel² have emphasized a panphlebitis as characteristic, but they note that the involved veins may not be recognized unless a special stain is used to demonstrate the elastic tissue in their walls.

Poisons

Various ingested corrosives leave their mark on the stomach as well as on the mouth, pharynx, and esophagus. The effects vary with the type and strength of the poison. Certain powerful poisons such as phenol and mercuric chloride cause immediate death and fixation of the gastric mucosa. The fixed tissue is firm, grayish white or brownish, and microscopically the cells appear well preserved. Little or no inflammatory reaction is evident, due to the rapidity with which death occurs.

Strong acids, such as hydrochloric and sulfuric, burn the tissues, which thus appear of yellowish or brown color, necrotic and hemorrhagic. Action on the blood in contact with the acid results in dark brown pigmentation due to hematin formation. Microscopically the tissue appears massively necrotic and disintegrated. The degree of inflammatory reaction depends on the period of survival after ingestion of the poison.

Strong alkalis, such as lye and lysol, also produce necrosis, with softening and discoloration, though the pigmentation may be less marked.

Various weaker corrosive poisons result in lesser degrees of the same type of change, with more opportunity for the development of marked inflammatory reaction.

Gastritis

An **acute gastritis** may be caused by various irritant foods and alcoholic drinks as well as by poisons. **Chronic gastritis** occurs in hypertrophic and atrophic forms.

Chronic hypertrophic gastritis is characterized by thickening of the mucosa and submucosa. The lining of the stomach is excessively rugose, or even polypoid. There is a hyperplasia of the mucosal epithelium, and in the submucosa there is a connective tissue increase with infiltration of chronic inflammatory cells.

Chronic atrophic gastritis is a nonspecific change due to inflammation and gastric injury in general. It may be particularly prominent in chronic alcoholism, chronic pellagra, and pernicious anemia. The normal rugae of the stomach are less prominent or absent, the mucosa is thin, and the stomach dilated. Microscopically, the mucosa is atrophic, with scarcity of mucosal glands, and increase of leucocytic infiltration and lymphoid aggregation in the mucosa and submucosa. The mucosa of the pylorus and fundus may be metaplastic, and transformed to an intestinal type, and there may be a change of parts of the mucosa of the fundus to a pyloric type (pyloric gland heterotopia). The interglandular connective tissue and the muscularis mucosa are thickened. A rare squamous metaplasia of the mucosa has been described by Sailer.⁶ There is no evidence that chronic atrophic gastritis predisposes to carcinoma of the stomach.⁶

In pernicious anemia there is an extreme atrophy involving all coats of the stomach wall. This change is localized in the upper two-thirds of the stomach and does not affect the pyloric antrum or duodenum. In the involved area the stomach wall is extremely thin, but there is an abrupt transition to normal thickness at the junction with the pyloric mucosa. In the involved area only a few scattered glands remain, the specialized oxyntic and peptic cells having entirely disappeared. Absence of inflammatory changes suggests that a purely atrophic process has occurred. These changes appear to be the morphologic basis of the achylia gastrica present in pernicious anemia.

Bezoars

Bezoar⁷ is a term applied to an accumulation of foreign material in the stomach and intestine. There are four varieties: (1) trichobezoar, or hair ball; (2) phytobezoar, or food ball; (3) trichophytobezoar, a combined hair and food ball; and (4) shellac bezoar, or concretion.

Pyloric Obstruction

In adults, stenosis and obstruction at the pylorus may result from the contracting scar of an ulcer, or from car-

cinoma. The stomach becomes greatly dilated, and filled by stagnant food and fluid. Persistent vomiting results in loss of chlorides and acid, and production of so-called gastric

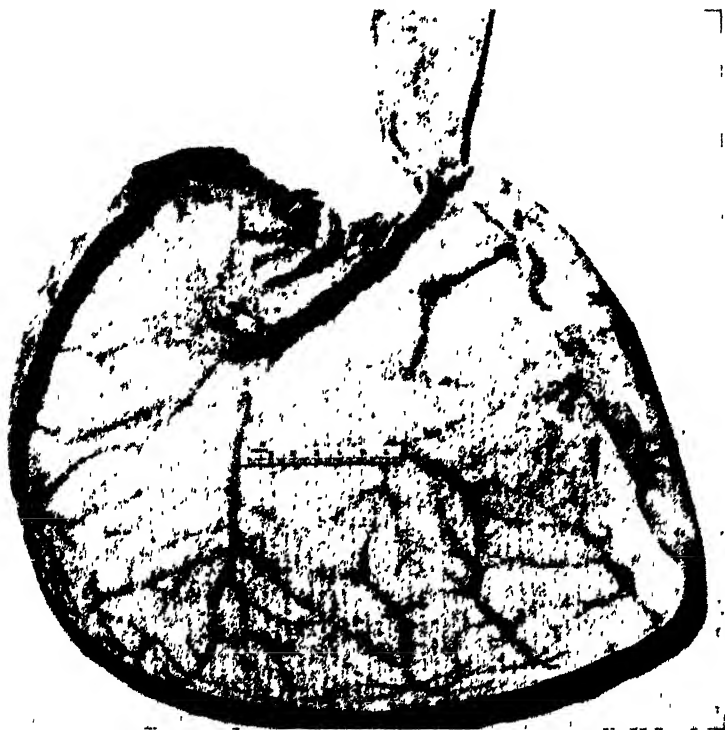


Fig. 213.—Pyloric obstruction due to carcinoma of stomach. The tumor involves the lesser curvature near pylorus. Note the dilatation and thinning of the walls of the stomach and esophagus proximal to the obstruction. (Courtesy Dr. H. C. Schmeisser.)

tetany—i.e., alkalosis and a chloride insufficiency occur. Increase in nonprotein nitrogen of the blood and evidence of renal insufficiency may be present. The kidneys show marked tubular degeneration, and often calcium deposits in the degenerated tissue. Other obstructions high in the intestinal tract produce a similar result.⁸

Peptic Ulcer

The term peptic ulcer refers to ulceration in areas which may be acted upon by acid gastric juice, i.e., the stomach.

first portion of duodenum, and, following gastrojejunostomy, the jejunum. Acute ulcerations or erosions are superficial and often hemorrhagic areas of mucosal loss. These common acute ulcers heal easily and give rise to little trouble. It is believed, however, that they may form the starting point for chronic peptic ulcers. Chronic peptic ulcers are more important than the acute forms because of their persistence, annoying symptoms, and the complications of hemorrhage, perforation, and malignant change. The term peptic ulcer, when unqualified, usually refers to this serious chronic type.



Fig. 214.—Chronic ulcer of stomach. (Courtesy Dr. H. C. Schmeisser.)

Acute Ulcer.—Acute ulcers or erosions are quite common and may be produced by a variety of injuries, such as coarse or excessively hot foods, septicemias, burns of the skin, etc. Many are probably of embolic origin. The variety complicating extensive superficial burns is known as a Curling ulcer. Found in only a small proportion of fatal burns, it is most common in the duodenum but also occurs in the stomach or intestine. Acute hemorrhagic ulcerations of the stomach or intestine occasionally complicate lobar pneumonia (Dieulafoy's erosion). Pneumococci have

been demonstrated in these lesions. Acute ulcers are usually small, involve only the mucosa and superficial layers of submucosa, and are often hemorrhagic. They usually heal readily but in certain areas and circumstances may become chronic. Acute ulcers are more frequent in the stomach than in the duodenum. The gastric ulcers apparently tend to heal more readily, while duodenal ulcers tend to be chronic.

Chronic Peptic Ulcer.—

ETIOLOGY.—Chronic ulcer is somewhat more common in the male, and in the white race in comparison with Negroes. The etiology and pathogenesis of chronic peptic ulcer are but poorly understood. The one factor of established importance is the **action of acid gastric juice**. Chronic ulcers develop only in areas of stomach and duodenum exposed to acid gastric juice. The jejunum exposed to acid gastric juice by a gastrojejunostomy may likewise develop a chronic ulcer, though ordinarily the jejunum is exempt. When there is achlorhydria, as in pernicious anemia, peptic ulcer does not occur. Excessive acidity (hyperchlorhydria) is common but not invariable in individuals with peptic ulcer.⁹ Caffeine-containing beverages cause prolonged increase in output of gastric acid and possibly contribute to the pathogenesis of ulcer in susceptible individuals.¹⁰ An intestinal extract containing *enterogastrone*, which inhibits gastric secretion and motility, has been effective in preventing development of experimental ulcers of peptic ulcer type in animals.^{10a}

Various other factors of uncertain importance have been debated. Numerous causes produce acute ulcerations or erosions. Virchow suggested the importance of **changes in vascular supply** of the mucosa, possibly by thrombosis or embolism. This circulatory theory still has adherents. Sclerotic changes are commonly found in blood vessels in the area of the ulcer, but usually they are considered secondary. **Localized infection**, particularly by certain strains of hematogenous streptococci, has been supported by Rosenow and others. **Influence of the nervous system** was noted by Rokitsansky and has been supported by the observations of Cushing, who noted peptic ulceration following disturbances of the hypothalamic region or diencephalon. Nuclei controlling secretory and vasomotor gastric functions appear to be located in the diencephalon. Stimulation of this

center or of the parasympathetic fibers passing from it to the stomach may cause hemorrhagic erosions or ulcers. A **constitutional tendency** or an "ulcer type" of individual has been noted by clinicians.

Various factors have been thought to prevent healing once the ulcer is established. These include hyperacidity and stasis, the traumatic effects of food, and the pull of muscle about the ulcer. The rather constant location of gastric ulcers on the lesser curvature has caused emphasis on functional and anatomic factors. Contraction of oblique muscle fibers forms a groove (*Magenstrasse*) along the distal part of the lesser curvature along which food or liquid may be forced without mixing with the rest of the gastric content. About 95 per cent of gastric ulcers are located in the *Magenstrasse*. This region, in comparison with other parts of the gastric mucosa, is exposed to more trauma, lacks protective mucin production, and is subjected to greater muscle traction.

GROSS APPEARANCE.—Peptic ulcers are highly constant in location, being found in the pyloric portion of the stomach, most commonly on the posterior wall near the lesser curvature, and in the first portion of the duodenum proximal to the ampulla. The gastric ulcers are usually situated a few centimeters proximal to the pyloric ring. Ulcers right at the pylorus are more commonly carcinomatous. Duodenal ulcers occur in the first portion (duodenal bulb) on the anterior or posterior wall. Peptic ulcers are usually single but may be multiple.

The ulcers vary in size from a few millimeters to 3 centimeters in diameter. They do not tend to extend and become very large. Large ulcers of the stomach are usually carcinomas rather than chronic peptic ulcers. An ulcer in the duodenum is practically never a carcinoma.

The chronic ulcers appear as indurated, deep, punched-out or funnel-shaped areas. The proximal or cardiac side of the gastric ulcer is usually steep, with overhanging edges, while the distal or pyloric side tends to be sloping or terraced. The base of the ulcer is covered by roughened, grayish, necrotic material, or may contain granular or blood-tinged exudate. Hyperemia or some fibrous thickening may be present around the edge of the ulcer. Variable degrees of fibrosis and distortion of the organ develop. When marked fibrosis spreads around the stomach, contraction tends to produce an hourglass deformity. Fibrous adhesion to adjacent organs, such as pancreas or liver, may be

present. Fibrosis about a duodenal ulcer shortens the distance between the pyloric ring and the opening of the ampulla.

MICROSCOPIC APPEARANCE.—At the edge of the ulcer, the mucosal and muscular layers end rather abruptly, though there may be some overhanging of the epithelium. Occasionally there is some downward proliferation of the marginal epithelium, producing an appearance which should not be confused with malignancy.

The whole thickness of the floor of the ulcer is composed of fibrous scar tissue, the muscle layers usually being completely gone. Over this fibrous base are successive layers of granulation tissue, necrotic and hyalinized material, and of exudate. Inflammatory cells may be found not only in this layer of exudate on the surface, but also in the granulation tissue and about the edges. Blood vessels in the base often show inflammation in early ulcers, and later intimal thickening, with narrowing or even obliteration of the lumen.

When healing occurs, it is by organization and fibrosis, the mucosa from the edges growing inward to cover the area. Contraction of the scar tissue sometimes produces an hourglass deformity of the stomach or pyloric stenosis.

COMPLICATIONS.—The complications and sequelae of peptic ulcer include hemorrhage, perforation, malignant change, and scar contraction with pyloric stenosis or deformity of the stomach.

Small hemorrhages commonly accompany peptic ulcers. Repeated small hemorrhages produce secondary anemia. A severe or even fatal hemorrhage may follow erosion of a larger vessel. Endarterial changes in the vessels of the base protect against this to some extent. On the other hand, the vessel walls, being held in rigid scar tissue, may be unable to retract following erosion.

Perforation results when the ulcer continues to penetrate deeply. Perforation into the peritoneal cavity produces shock and soon results in peritonitis. In other older ulcers adherent to some surrounding structure, perforation may occur into the adherent organ.

RELATIONSHIP TO CARCINOMA.—Malignant change may develop in a chronic gastric ulcer, but this is extremely rare in duodenal ulcers. While the frequency of this occurrence in gastric ulcer is debated, the consensus is that less than 5 per cent of gastric ulcers undergo malignant change.

In an ulcerating gastric cancer, evidence that it arose from a previously benign chronic ulcer is given by: (1) complete destruction of the muscle layers of the stomach in the base of the ulcer; (2) fusion of the muscularis mucosa and muscle wall at the margin of the ulcer; (3) intimal thickening of blood vessels; (4) the presence of carcinoma in only one part of the wall and its absence in the base of the ulcer and in other portions of the wall.

Distinguishing points of benign and malignant gastric ulcers are given in Table XIII. Sometimes the distinction is impossible without microscopic examination and application of the usual histologic criteria of malignancy.

TABLE XIII

COMPARISON OF BENIGN AND MALIGNANT GASTRIC ULCERS

	ULCERATING CARCINOMA	CHRONIC ULCER
Duration	History less than two years	History often more than two years
Age	More frequently past forty	Frequently begins under forty
Size of ulcer	Usually over 2.5 cm. in diameter	Diameter usually less than 2.5 cm.
Position	Usually at or very near pylorus	Commonly 2 to 3 inches from pylorus
Edge of ulcer	Raised, rounded	Sharp, punched out, terraced on pyloric side

Tumors of the Stomach

Benign.—Benign tumors of the stomach are uncommon, and of little clinical significance unless they obstruct the pylorus. The mucosa may be involved by papilloma or a polypoid adenoma. Fibroma, myoma, and lipoma also occur.

Carcinoma of the Stomach.—Malignant tumors of the stomach are important because of their frequency. Carcinomas of the stomach constitute 20 to 35 per cent of all malignancies and are the commonest type of carcinoma in the male.

TYPES.—Carcinoma of the stomach occurs in three main gross forms: (1) papillary, or polypoid; (2) ulcerating; (3) scirrhus or infiltrating. A mucoid or gelatinous type also occurs, as a variety of the above types. The pyloric region, particularly the lesser curvature, is the common site, about one-half of gastric cancers originating in this situation. The localized scirrhus or ulcerative type usually occupies this

position. The diffuse scirrhus type (*linitis plastica*) is rare, constituting less than 5 per cent. Carcinoma of the body, fundus, and cardia of the stomach is usually a soft, papillary tumor.

The papillary or polypoid carcinoma is a soft, bulky tumor which projects into the cavity of the stomach. It is usually an adenocarcinoma or carcinoma simplex. The size of the tumor may be large before many symptoms are produced. The surface tends to become ulcerated and infected, and it bleeds easily. The tumor infiltrates the submucosa and muscularis, but the course of this type may be relatively slow. This circumscribed polypoid form constitutes about 8 per cent of gastric cancers and is a relatively favorable form for surgical removal.



Fig. 215.—Diffuse scirrhus carcinoma of stomach (*linitis plastica*). Note the marked diffuse thickening and contraction of the wall. (Courtesy Dr. H. C. Schmeisser.)

The ulcerating variety commonly involves the pyloric region and lesser curvature. It is the most frequent form of gastric carcinoma. Distinction from a benign chronic ulcer may be difficult. It is more than 2.5 cm. in diameter and has raised rounded edges. Microscopically it is usually a car-

cinoma simplex, the cells forming columns or solid masses. Infection, hemorrhage, and pyloric obstruction may complicate this variety.

The **scirrhus** infiltrating carcinoma of the stomach begins at the pylorus, tends to encircle this region and extend proximally. No localized tumor is present, but the involved portion of the stomach is very thick walled and firm. Stenosis and obstruction of the pylorus are usually seen. The proximal extension toward the cardia may be for only a short distance, or the whole stomach wall may be involved. This diffuse infiltrating type (**linitis plastica** or leather-bottle stomach) results in a small, very thick-walled stomach. Histologically, the scirrhus carcinoma is characterized by very abundant connective tissue stroma. The malignant epithelial cells may be quite scarce and even difficult to find. Rarely, a similar gross change in the stomach may result from chronic inflammation, e.g., syphilis (see p. 467). Carcinoma of the stomach usually stops abruptly at the pylorus, so that the duodenum is rarely involved.

Multiple gastric polyposis may be neoplastic or of inflammatory origin. Malignant changes are prone to occur.¹⁶

Mucoid degeneration may occur in any of the varieties of gastric carcinoma, either in small localized areas or involving the whole tumor. The mucoid areas grossly appear translucent and gelatinous. Accumulation of the mucoid in the cytoplasm of the cancer cells displaces the nucleus to one edge, giving the cell a signet ring appearance. This same appearance may be found in metastases.

SPREAD AND METASTASIS.—The scirrhus forms of gastric carcinoma spread chiefly in the stomach wall, but metastasis to other organs is unusual. The soft forms spread to adjacent draining lymph nodes, to liver, peritoneum (pouch of Douglas and ovaries), and sometimes by blood stream.

Not only local lymph nodes, but also the left supraclavicular nodes are frequently invaded, where the involvement can often be determined clinically by palpation and biopsy. Peritoneal spread may produce ascites, and involvement of the pouch of Douglas may be evident by rectal palpation. Ovaries may be involved by bilateral (Krukenberg) tumors.

Sarcoma of the Stomach.—Sarcoma of the stomach is rare. The varieties include fibrosarcoma or spindle-cell sarcoma, round-cell sarcoma, and lymphosarcoma. The round-cell sarcoma may be difficult to differentiate from a highly anaplastic

carcinoma. Lymphosarcoma forms an intramural tumor, is similar to lymphosarcoma elsewhere, and is markedly radio-sensitive.

Carcinoma of the Duodenum

The duodenum is a rare site for cancer, even as a malignant change in a chronic duodenal ulcer. Most carcinomas of the duodenum arise at or about the ampulla of Vater and hence usually obstruct the bile and pancreatic ducts, with the early appearance of jaundice. Some probably originate from bile duct epithelium rather than from duodenal mucosa, and others from aberrant pancreatic tissue.¹⁸

INTESTINAL TRACT

The main types of diseases of the small and large bowel are: (1) inflammatory and infective conditions, including inflammations of diverticula and of the peritoneum, (2) obstructions, and (3) tumors.

Inflammation of the Intestinal Tract

Inflammations may involve large portions of the tract, but often one region is affected exclusively or more prominently, so that the terms enteritis (small intestine), ileitis, appendicitis, colitis, sigmoiditis and proctitis (rectum) may be used to indicate inflammation of the particular region. The causes are of two main groups: (1) poisons, either endogenous (e.g., in uremia) or exogenous (mercury poisoning, botulinus food poisoning), and (2) infections (typhoid, dysentery, cholera, tuberculosis, etc.).

The inflammation may be: (1) catarrhal, i.e., a superficial inflammation involving the mucosa of the bowel; (2) follicular, in which in addition to catarrhal inflammation there is a marked hyperplasia of the lymph follicles; (3) diphtheritic, characterized by the formation of a false membrane composed of necrotic mucosa and a fibrinous exudate; (4) ulcerative, in which sloughing of necrotic areas and ulceration are often of distinctive nature. Some types of infection of the bowel may be catarrhal, diphtheritic, or ulcerative, etc., depending on their stage or degree of severity.

INTESTINAL INFLAMMATION DUE TO POISONS

Endogenous.—**Uremia** is accompanied by intestinal lesions in about 20 per cent of the cases. The earliest changes in the mucosa are areas of hyperemia and edema, followed by

hemorrhage, necrosis, diphtheritic change, sloughing, and ulceration. Uremic ulcers are most common in the lower ileum, cecum, and ascending colon, but they also occur in other parts. The change is probably due to localized interference with circulation to the involved area of bowel, and



Fig. 216.—Hemorrhagic colitis.

sclerotic or necrotic changes in blood vessels are often evident in the affected region. Irritation from excessive ammonia in the intestinal content, due to excretion of excess urea, also has been suggested as a causative factor.

Exogenous.—Poisoning by heavy metals, such as mercury bichloride and other corrosives, may produce an intense

TABLE
INFLAMMATIONS AND ULCERATIONS

	ETIOLOGY AND PATHOGENESIS	REGION OF BOWEL INVOLVED PRE-DOMINANTLY	NATURE OF LESION
Chemical poisons	Corrosive action of ingested salts of mercury and other heavy metals	Ileum and colon	Hemorrhagic and diphtheritic
Uremia	Localized blood vessel changes; (?) ammonia poisoning	Lower ileum, cecum and ascending colon	Hemorrhagic, diphtheritic and ulcerative lesions
Burns	In 1 to 6 per cent of fatal burns; possible relation to adrenal damage	First part of duodenum, stomach, and small intestine in order of frequency	Acute, ulcerative
Typhoid and paratyphoid	Organisms ingested in contaminated water and food; generalized infection	Ileum—Peyer's patches and solitary lymph follicles	Hyperplastic and necrotic; involvement of lymphoid tissue
Bacillary dysentery	Ingested dysentery bacilli produce localized infection of intestine	Large intestine, especially distal portion	Diphtheritic inflammation, with widespread necrosis and abundant exudate
Amebic dysentery	Ingested <i>Endameba histolytica</i> locally affect intestine	Large intestine	Local invasion and tissue lysis by parasite
Chronic ulcerative colitis	? Chronic form of bacillary dysentery	Large intestine, especially distal portions	Chronic ulcerative inflammation
Cholera	Ingested cholera vibrios of Koch produce infection of intestine	Whole intestinal tract, but particularly colon	Acute catarrhal inflammation, reddening of mucosa, sometimes hemorrhages
Regional enteritis	Etiology uncertain ? tuberculosis ? local form of sarcoid ? lymphopathia venereum	Ileocecal region	Marked thickening of a segment of ileum
Tuberculosis	Usually secondary to pulmonary lesion, due to swallowing sputum. Occasionally primary from infected milk or food	Ileocecal region—starts in lymphoid tissue	Tubercle formation in lymphoid tissue of bowel. Sometimes hyperplastic with thickening of bowel wall
Actinomycosis	Ingested ray fungus	Ileocecal region and appendix	Suppurative and ulcerative, with thickening of bowel wall
Lymphogranuloma venereum	Virus. Frei reaction positive	Usually large intestine	Chronic suppurative and granulomatous

XIV

OF THE INTESTINAL TRACT

CHARACTER OF ULCERS	MICROSCOPIC	COMPLICATIONS
Ragged, small, superficial. May be coalescing and extensive		
No specific form, hemorrhagic, multiple, sometimes extensive	Hyaline thickening, inflammation and necrosis of small arteries in affected area	
Acute, usually single, may be long and narrow		Hemorrhage, perforation
Ulcers involve Peyer's patches, oval, in long axis of bowel	Proliferation of large mononuclear phagocytic cells	Perforation, hemorrhage
Shallow, ragged, very numerous and coalescent, not undermined	Superficial fibrino-purulent exudate	Dehydration, stenosis may follow healing
Undermined edges; flask-shaped on section	Amebae in tissues. Leucocytic infiltration when secondarily infected	Perforation, liver abscess
Extensive ragged, chronic, coalescing ulcerations surrounding islands of hypertrophic mucosa		Stricture of bowel wall. Sometimes malignant change in polypoid mucosal islands
No ulcers but superficial desquamation of surface epithelium	Loss of epithelium from mucosa	Extreme dehydration
Not specific	Extreme thickening of submucosa. Sarcoid-like aggregates of epithelioid and giant cells	Obstruction of bowel, mesenteric lymph nodes affected. Perforation rare
Affect lymphoid tissue but tend to encircle bowel	Caseous necrosis epithelioid cells, giant cells, lymphoid cells	Stenosis of gut, perforation and peritonitis
Not specific	Suppuration, characteristic ray fungus in lesions	Pylephlebitis; chronic draining sinus or fistula
Not specific	Often not characteristic. Focal abscesses	Obstruction of lumen

hemorrhagic and diphtheritic inflammation of the bowel. Ileum and colon are most markedly involved (see Chap. IX).

INTESTINAL INFLAMMATIONS DUE TO INFECTION

Among the most important intestinal infections are those due to the coli-typhoid-dysentery group of organisms. This group consists of aerobic Gram-negative bacilli. One division of the group, distinguished by inability to ferment lactose, consists of highly pathogenic organisms, such as those of typhoid, paratyphoid, and dysentery. A second division, composed of lactose fermentors, includes the colon bacillus and closely related organisms. They are of very low pathogenicity.

Typhoid Fever.—Infection with the typhoid bacillus is characterized by involvement of lymphoid and reticulo-endothelial tissues, with hyperplasia of large mononuclear phagocytic cells. It is in all cases a generalized infection, but involvement of the lymphoid tissue of the intestine (Peyer's patches and solitary lymph follicles) is usually the most prominent feature, and ulceration there gives rise to the most dangerous complications of perforation and hemorrhage.

The organisms are ingested with water, milk, or food which has been contaminated, usually by chronic carriers. The febrile illness often has marked mental clouding and toxic symptoms in addition to intestinal disturbances, and it lasts about four weeks. Blood culture is usually positive during the first week, less regularly so later. Stool culture is more frequently positive during the second and third weeks. Urine culture is positive in about 20 per cent of cases in the third and fourth weeks. The Widal reaction, which is the demonstration of specific agglutinins in the patient's serum, is usually positive after the first week. This test may be invalidated as a diagnostic procedure if the patient has had a recent inoculation with typhoid vaccine, which may produce a positive reaction. At autopsy, the organisms are most easily isolated from spleen or gall bladder. The leucopenia which occurs, with decrease in the number of granulocytes and relative increase in nongranular white blood cells, is in accordance with the body's reaction to the organism, i.e., proliferation of mononuclear cells rather than exudation of polymorphonuclear leucocytes.

INTESTINAL LESIONS.—The lower ileum and cecum, where lymphoid tissue is most abundant, is involved earliest and most severely. The more proximal parts of the small intestine and the more distal parts of the large intestine show a

later and less severe reaction. Goodpasture¹⁹ has demonstrated in early cases the growth of a small Gram-negative form of the organism in young plasma cells of the lymphoid follicles. The early changes in Peyer's patches and lymphoid follicles are congestion and edema, followed soon by a great proliferation of mononuclear leucocytes, the characteristic cells of typhoid. These involved lymphoid regions stand out as irregular projecting prominent areas on the mucosal surface. The large mononuclear cells in the lesions are actively phagocytic, and in their cytoplasm can be seen remnants of ingested lymphocytes, plasma cells, and sometimes the large Gram-negative typhoid bacilli.

At about the seventh to tenth day necrosis begins in the affected patches. Tiny necrotic areas slough off leaving small ulcers which by their coalescence form rounded or oval areas of ulceration having the size, shape, and situation of the Peyer's patches. The long axis of these ulcers is in the direction of the long axis of the bowel, in contradistinction to tuberculous ulcers which tend to encircle the gut.

This process of ulceration, particularly if rapid, may result in hemorrhage. The ulcers usually involve only the mucosa and submucosa, but deeper extension and perforation may occur, particularly as the result of secondary infection. Perforation is most apt to occur in the lower ileum, where the lesions are earliest and most severe. Generalized peritonitis follows, except in cases of slower perforating processes which allow a walling off and localization of the peritonitis.

On recovery, surface epithelium grows over the ulcerated area, but there is little regeneration of the glandular epithelium or lymphoid tissue. There is no scar formation or contraction of the bowel.

LESIONS IN OTHER ORGANS.—While intestinal lesions are usually primary and predominant in typhoid fever, the infection is a generalized one, and various other organs, such as lymph nodes, spleen, liver, bone marrow and gall bladder, are rather constantly involved. The reaction tends to be similar everywhere, with proliferation of large mononuclear cells and foci of necrosis. The necroses are due mainly to the endotoxins of *Eberthella typhi*, but vascular blockage by accumulated mononuclear cells is a contributing factor.

The spleen is enlarged up to 400 or 500 grams. It is red, soft and exceedingly engorged with blood. In addition to this extreme congestion, collections of large mononuclear cells are seen microscopically. Small focal areas of necrosis may be present.

The liver likewise shows small focal necroses, irregularly distributed in the lobules.

Mesenteric lymph nodes also have microscopic necroses and great accumulation of large mononuclears. Similar changes may be found in bone marrow, where the formation of granulocytes is in abeyance.

The gall bladder is usually infected, and the organisms can be cultivated from the bile. Morphologic change in the gall bladder usually is slight, but acute cholecystitis may accompany or follow typhoid. A focus of infection may remain here, however, and excretion of organisms by way of bile and intestinal tract results in a chronic carrier of the disease.

Cloudy swelling and even fatty degeneration affect the heart, liver, and kidneys in typhoid fever as in other acute infections. Zenker's degeneration of voluntary muscle is not uncommon. Rarer complications of typhoid fever include meningitis, suppurative periostitis or osteomyelitis, hemorrhagic pneumonia, and thrombosis of veins of the legs.

Paratyphoid Fever.—The illness of paratyphoid infection is similar to that of typhoid, though of shorter duration, less severe, and with lower mortality. The lesions produced are essentially similar but of less severe degree. There is a somewhat greater tendency to pus production and abscess formation. The salmonella group of organisms are causative agents in certain types of food poisoning.

Bacillary Dysentery.—Dysentery is a term loosely used to indicate diarrhea with pus, blood, or mucus in the stools. Several unrelated conditions may thus be included under this term. The important types of dysentery are due to the *Shigella dysenteriae*, and to *Endamoeba histolytica*.

There are several varieties of dysentery bacilli, which may be distinguished by fermentative and antigenic reactions. They produce an endotoxin which has a local effect on the intestinal mucosa, and some also produce an exotoxin which may affect the nervous system.

The dysentery organisms reach the intestinal tract with contaminated food and drink. Dysentery is endemic but also tends to break out in epidemics, particularly in hot weather and when many individuals live together under crowded and unhygienic conditions. An acute febrile illness lasting six to eight weeks results, but the infection is localized to the bowel, and positive cultures cannot be obtained from the blood. Repeated flare-ups or even a chronic condition may occur.

The large intestine is involved almost exclusively, specific lesions being rare in other organs. The distal parts of the

colon are more severely affected. Occasionally the terminal ileum becomes involved. The lesion is of a diphtheritic or even membranous type, with necrosis and desquamation of surface layers and abundant fibrino-purulent exudate. In some very acute cases, death occurs from toxemia before any marked lesions have developed in the bowel. In most cases, however, there are widespread necroses of the mucosa of the large intestine and abundant exudate. Sloughing of necrotic areas leaves an extremely ragged ulceration of the colon. The ulcers are usually shallow, not undermined, and vary a great deal in size and shape. Their coalescence denudes large areas leaving only occasional islands of intact mucosa. Marked diarrhea, excessive fluid loss, dehydration, and exhaustion accompany this condition of the bowel. Severe hemorrhage is uncommon. Perforation also is unusual and usually results in localized rather than generalized peritonitis.



Fig. 217.—Bacillary dysentery, large intestine. (Courtesy Dr. H. C. Schmeisser.)

Microscopic study shows the necrosis or ulceration of the mucosa, with exudate on the surface. All layers of the bowel wall are edematous and infiltrated by polymorphonuclear leucocytes, but the submucosa is most markedly involved. Recovery is accompanied by healing of the ulcers, sometimes

with scar formation and stenosis of the bowel. In healing, small mucosa-lined cysts may be formed, which continue to harbor the organisms.

Amebic Dysentery.—*Endamoeba histolytica* infection of the large intestine produces large, undermined, and flask-shaped ulcerations. The amebae can be identified microscopically in the adjacent tissues. Leucocytes are present when there is secondary infection. For detailed consideration see page 162.

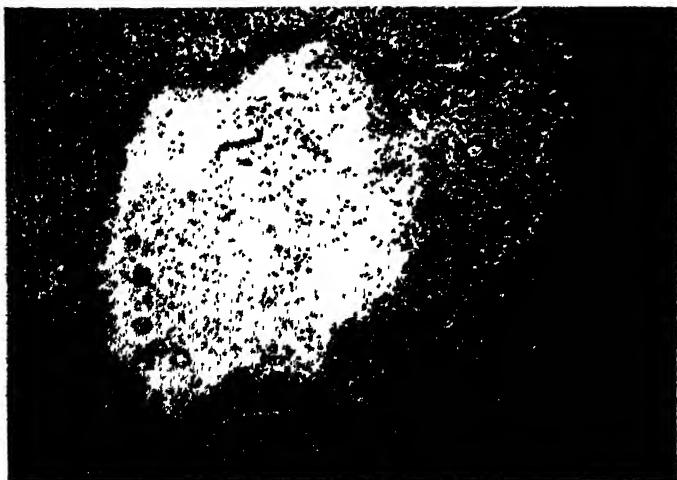


Fig. 218.—*Balantidium coli* infection of bowel. (U. S. Army Medical Museum.)

Balantidial Dysentery.—A rare ulcerative dysentery is due to the ciliated protozoan parasite, *Balantidium coli*, the natural host of which is the pig. The parasites invade the mucosa of the large intestine, and may produce chronic ulcers, sometimes deep and undermined. Lymphocytes, eosinophiles, and neutrophils may form a mild inflammatory exudate. The parasites are easily recognized in the lesions by their large size (50 to 100 microns) and the large, dark elongate nucleus (Fig. 218).

Cholera.—Cholera is an Asiatic and tropical disease caused by the Cholera vibrio or comma bacillus. It spreads in epidemic fashion, particularly by contamination of water and food. The infection is practically limited to the intestinal tract, where there is an acute catarrhal inflammation, with

marked reddening of the mucosa. Profuse diarrhea, with flakes of whitish material in the watery stools (rice water stools), is characteristic and results in profound dehydration.

Chronic Ulcerative Colitis.—Chronic ulcerative colitis is of debatable etiology but is usually considered as a specific entity. There is considerable evidence that some cases at least are chronic forms of bacillary dysentery.



Fig. 219.—Chronic ulcerative colitis. (Courtesy Dr. H. C. Schmeisser.)

The large intestine is involved, the rectum and sigmoid being affected earliest and most severely. Hyperemia and edema of the mucosa are followed by the appearance of small areas of necrosis and ulceration. Their coalescence produces large irregular and ragged ulcerations. Strips and tags of mucosa surrounded by the ulcerations become edematous and hyperplastic, projecting as inflamed polypoid masses. Eventually the bowel wall undergoes a considerable fibrotic thick-

ening, and the ulcers heal by scar tissue. Stricture or stenosis of the bowel is thus a common complication, but perforation or severe hemorrhage is rare. Malignant change may occur in the polypoid mucosa.

Regional Ileitis.—Regional ileitis (Crohn's disease) is a hyperplastic granulomatous condition affecting distal portions of the ileum. It is characterized grossly by a marked regional thickening of the bowel wall with corresponding stenosis of the lumen, mucosal ulceration, and enlargement of regional mesenteric lymph nodes. Histologically, its unique feature consists of focal masses of epithelioid and giant cells in the involved submucosa and in mesenteric lymph nodes. These lesions may occur in small numbers or even be entirely absent. Important clinical features are a palpable mass in the abdomen, signs of chronic obstruction, abdominal pain, and loss of weight.

The etiology is unknown, although it has been ascribed to a wide variety of infective, toxic, and vascular factors. Histologic similarity suggests a possible relationship to Boeck's sarcoid.²³ It is to be distinguished from the granulomatous lesions of tuberculosis and actinomycosis, which also commonly involve the ileocecal region, by the different histologic picture and demonstration of the specific causative organisms of the latter conditions. Lymphogranuloma inguinale may involve the bowel and is differentiated by the presence of a positive Frei reaction, its microscopic appearance (see p. 151), and its usual involvement of colon rather than ileum.

Regional ileitis appears grossly as a garden-hose thickening of a segment of ileum, either at or within a few feet of its termination. In its acute stage the involved area is red and edematous. Later, it tends to be rigid, firm, fibrous, and ulcerative. The bowel is dilated proximal to the constricted lumen of the involved segment. The adjacent mesentery contains enlarged lymph nodes. Perforation may occur but the effects are usually limited by peritoneal adhesions.

Microscopically, the main feature is extreme thickening of the submucosa. This begins with a marked hyperplasia of lymphoid tissue, and the development of noncaseating aggregates of epithelioid cells and multinucleated giant cells. Tubercle bacilli cannot be demonstrated in these lesions. Similar sarcoid-like lesions are often present in the enlarged mesenteric nodes. Obstructive lymphedema is also constantly present in the thick submucosa. Ulcerations of various depth develop, floored by granulation tissue.

Eventually a diffuse cellular infiltration involves the bowel wall, with thickening of the muscular coat, and adhesions of the serosa.

Tuberculosis.—Tuberculous infection of the intestine may be primary, the organisms being ingested with milk or other food. More commonly it is secondary to a pulmonary lesion, due to swallowing of infected sputum. A considerable proportion of fatal cases of pulmonary tuberculosis show intestinal lesions.

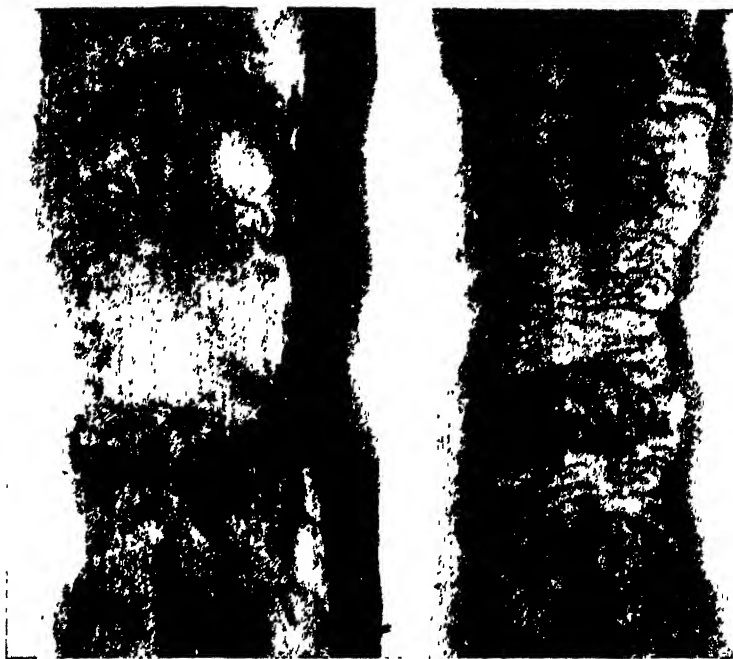


Fig. 220.—Tuberculous enteritis. Note the oval ulcers tending to encircle the bowel. The change in the serosal surface is seen on the left. (Courtesy Dr. H. C. Schmeisser.)

The lesions begin and are most common in the lower ileum, but from there extend upward and downward to involve small intestine and colon. The lymphoid tissue of the bowel is affected, and yellowish areas of caseous necrosis develop in the mucosa and submucosa. Ragged ulcers result from sloughing of this necrotic material. The lesions extend by lymphatics which run laterally, encircling the gut. Hence the ulcerative

lesions tend to be of elliptical shape, extending laterally and partially encircling the bowel. When such an ulcer is deep and extensive, its healing may produce marked contraction and stenosis of the bowel. The microscopic appearance is similar to that of tuberculosis elsewhere, with caseous necrosis and lymphoid, epithelioid, and giant cells. Perforation of a tuberculous ulcer is uncommon and usually results only in a localized peritonitis or abscess formation, as peritoneal reaction has walled off the area. Severe hemorrhage rarely occurs because blood vessels in the lesions are involved by periarteritis and endarteritic changes as they are in tuberculous pulmonary cavities. Occasionally a hyperplastic form of tuberculosis occurs around the ileocecal region, with marked thickening of the bowel wall. Such lesions may be difficult to distinguish grossly from regional enteritis and tumors.

Actinomycosis.—The ileocecal region or appendix is one of the common sites for actinomycosis. Characteristic features are thickening of the bowel wall, ulceration, and suppurative areas containing the ray fungus. Pylephlebitic spread to the liver is a frequent complication. Appendectomy is apt to be followed by a chronic sinus or fistula, if the appendiceal infection was actinomycotic.

APPENDICITIS

Inflammation in the appendix has the same features and follows the same course as inflammation elsewhere. Its importance is due to its frequency as a serious surgical condition with a considerable mortality. Obstruction of the appendiceal lumen by fecoliths and interference with vascular supply are important features in its pathogenesis. Spread of the infection beyond the appendix is the factor which causes mortality, rather than the lesion in the appendix itself.

Etiology.—The full story of the cause of acute appendicitis is not yet known. The nervous strains and dietary habits of modern life have been vaguely invoked as predisposing factors. The essential thing in causing the wall of the appendix to react with inflammation is invasion by bacteria. The common organisms in the inflamed appendix are colon bacilli and varieties of streptococci, organisms commonly found in the intestinal lumen. Obstruction and vascular occlusion are factors of tested importance in the etiology of appendicitis. They probably act by breaking down the resistance of the appendiceal wall to invasion by the potential pathogens in the lumen.²⁸

The importance of luminal obstruction has been reemphasized by the work of Wangensteen and his associates.²⁵ They have shown that an obstructed appendix having a normal mucosa may develop a secretory pressure approaching systolic blood pressure, thus presumably interfering with the blood supply of the tissue. Such obstruction may act as the exciting cause of typical acute appendicitis. The importance of occlusion of vascular supply to an area of the appendiceal wall has been shown by Felsen and Lewis.²⁶ A segmental, rather than diffuse, involvement of the appendix would seem to have such an origin.



Fig. 221.—Acute diffuse appendicitis with gangrene. (Courtesy Dr. H. C. Schmeisser.)

Morbid Anatomy.—Acute appendicitis is often classified as: (1) catarrhal, (2) diffuse, and (3) gangrenous. Catarrhal appendicitis is one in which the inflammation is limited to the mucosal and submucosal layers. It is usually a mild type, or an early stage of the diffuse type. In diffuse appendicitis the muscular and serosal layers are involved as well. In gangrenous appendicitis there is the added condition of necrosis.

The beginning of acute appendicitis is usually a superficial ulceration of the mucosa. Spread occurs from the mucosa to the serosa in a wedge-shaped area and then travels rapidly lengthwise in the muscular and serous coats. Grossly, the appendix appears swollen, the serosal vessels are congested, and the surface of the serosa has lost its normal shininess, or may be covered by discernible fibrinous exudate. The muscular walls are thick and edematous. The mucosa may show areas of hemorrhage and ulcerations. A cause of

luminal obstruction often is found in the form of a fecolith (a firm, dried, fecal concretion), or it may be due to marked fibrous thickening of a portion of the appendiceal wall. Over a large fecolith the wall is apt to be thin and gangrenous. Gangrenous areas show a grayish-green or black discoloration, have a thick flaky layer of fibrin on the surface, and often a small perforation.



Fig. 222.—Acute appendicitis. The lumen is distended and filled with pus. (Courtesy Dr. H. C. Schmeisser.)

Microscopically, the early stage of acute appendicitis is often difficult to discern, particularly if the section is not through exactly the right area. The normal lymphoid cellularity of the mucosa and submucosa may be confusing. Granular leucocytes are more easily distinguishable in early cases by the use of an oxydase stain.²⁷ Ulceration of the mucosa or a purulent exudate in the lumen may be seen if the section is

through the proper area. In most cases of acute appendicitis the diagnosis is obvious from the infiltration of leucocytes in the muscular and serous layers.

Complications of Acute Appendicitis.—Many milder cases of acute appendicitis subside without surgical interference, but in other cases spread of the infection may occur with serious or fatal results. Such spread is usually to the peritoneum as a result of gangrene or perforation. If there has been opportunity for the walling off and limitation of the infection to the region around the appendix, a localized abscess may result. This localized peritonitis is much less dangerous than the generalized peritoneal spread which quite commonly occurs. In some cases spread from the appendix is by infection of portal veins draining the inflamed organ (pylephlebitis) and leading to the production of multiple abscesses in the liver.



Fig. 223.—Fecalith of appendix. (Courtesy Dr. H. C. Schmeisser.)

Chronic Appendicitis.—Chronic appendicitis has been a subject of controversy because it is often difficult to correlate the clinical symptoms attributed to the appendix with the anatomic findings. In some cases there is evidence of obstruction, from a fecalith or other cause, but without any active inflammatory process discernible in the wall of the appendix. Very often the anatomic finding is a fibrous thickening of the submucosa and mucosa, with atrophy of the mucosal glandular elements, and with or without a hyperplasia of the submucosal lymphoid tissue. In its extreme degree such fibrosis may completely obliterate the lumen. This fibrosis is believed, in many cases, to be the end result or healed stage of previous recurring attacks of acute inflammation. An appendix with complete obliteration of the lumen

is unlikely to become inflamed again, but partial obliteration may predispose to recurrent inflammation.

Masson's studies²⁹ have indicated that in some cases the thickening of the submucosa and obliteration of the lumen are due largely to proliferation of smooth muscle bundles and nervous elements associated with Meissner's plexus, the so-called musculo-nervous complex of the appendix. Atrophy



Fig. 224.—Obliteration of lumen of appendix. (Courtesy Dr. H. C. Schmeisser.)

of lymphoid tissue and glandular mucosa tends to occur along with the hypertrophy and hyperplasia of sympathetic nerves and muscle fibers. Tiny, discrete neuromas may be formed in the submucosa. It is not known whether inflammation is the stimulus for this process.

A lymphoid type of chronic appendicitis has been described by Fausset.³⁰ Lymphoid tissue is a normal constituent of the submucosa of the appendix, and particularly in young in-

dividuals it may be very abundant, but in older people it gradually atrophies. There may be, however, a marked chronic hyperplasia of this lymphoid tissue, associated with atrophy of the glandular elements of the mucosa and gradual sub-mucosal fibrosis. The condition may progress to fibrous obliteration of the lumen.

Lesions of the Appendix in Measles.—In measles the lymphoid tissue of the appendix, as well as in the throat, spleen, and remainder of the intestinal tract, is markedly hyperplastic. In early stages there are characteristic giant cells in the mucosa and lymph follicles.

Oxyuris Vermicularis Infection of the Appendix.—In children pinworms commonly infect the appendix, where they may obstruct the lumen. In most instances they cause little damage, but in some cases may be associated with the clinical picture of acute appendicitis.^{31, 32, 33} (See p. 172.)

Mucocele of the Appendix.—Complete obstruction of the proximal portion of the appendix sometimes results in a cyst-like dilatation (mucocele) of the distal part. The contents of the dilated sac are a thick mucoid material. In some instances rupture of the mucocele may cause pseudomyxoma peritonei. This latter condition is more commonly a complication of ovarian pseudomucinous cystadenoma.

Diverticula of the Intestine

A diverticulum of the intestine may be true or false. A true diverticulum has all layers of the bowel in its wall, the common example being the congenital Meckel's diverticulum. False diverticula are acquired herniations of the mucosa through a weak place in the muscularis of the bowel. Their walls contain only mucosal and serosal layers. They occur in both small and large intestine, being particularly common in the latter.

Meckel's Diverticulum.—Meckel's diverticulum is due to persistence of the proximal portion of the omphalomesenteric duct, which normally atrophies during early fetal life. It is found in about 2 per cent of individuals. It varies up to 30 cm. in length but is usually about the size of a small finger. It is situated one to three feet proximal to the ileocecal junction. Its structure is similar to that of the bowel wall, but heterotopic tissue, such as gastric or duodenal mucosa, or pancreatic tissue may be found in it. Peptic ulcer, subject to the complications of hemorrhage and perforation, has been reported in such tissue.

The commonest lesion of a Meckel's diverticulum is inflammation. Pathologically, this is similar to appendicitis, which it may mimic clinically. More rarely, it may promote intestinal obstruction by intussusception or adhesions, or it may be the seat of a tumor.

Acquired Diverticula.—The common situations for diverticula are the duodenum and colon, but they also occur in the small intestine. These are commonly false diverticula, though some may have muscle fibers in their walls. In the small intestine they occur along the mesenteric attachment, whereas in the colon they are situated away from the mesenteric attachment between the tenia or longitudinal muscular bands of the colon. The descending and sigmoid portions of colon have the highest incidence. The protrusion often is into appendices epiploica, so that the diverticula are readily overlooked. They vary up to several centimeters in diameter. Microscopically, their wall is found composed of a thinned mucosa and serosa between which may be a few connective tissue and muscle fibers.

When present without complications, the condition is known as **diverticulosis**. The common complication is inflammation or **diverticulitis**. This is promoted by the lodging of fecal matter in the sacs. Spread of inflammation to surrounding tissue (**peridiverticulitis**) may occur also. The chronic inflammatory process causes thickening of the bowel wall and adjacent tissues, with constriction of the lumen of the bowel. The gross appearance may closely simulate that of carcinoma.

Stricture of the Rectum

A variety of inflammatory processes, scar contractions and tumors may cause rectal stricture. It is particularly common as a complication of lymphogranuloma inguinale in females. This virus infection spreads by lymphatics from the primary lesion on the genitals. The distribution of lymphatics in females is such as to involve perirectal tissue, whereas in the male, the spread is usually to inguinal lymphatics. The rectal involvement is a chronic progressive granulomatous inflammation which leads to serious stricture.

Pilonidal Sinus

Pilonidal sinus, or sacrococcygeal sinus, is a very common congenital lesion, believed to be a remnant of the neurenteric canal, or an infolding of the epithelial layer of skin. It occurs in the midline a few centimeters posterior to the anus, the

sinus extending inward toward a cystic cavity in the subcutaneous tissue above the sacrococcygeal vertebrae. Microscopically, the usual features are hair follicles or shafts, multinucleated giant cells of the foreign body type, and abundant lymphocytes and plasma cells. Troublesome recurrence is apt to follow incomplete removal or infection in adjacent tissue. Malignancy in a pilonidal sinus is extremely rare.

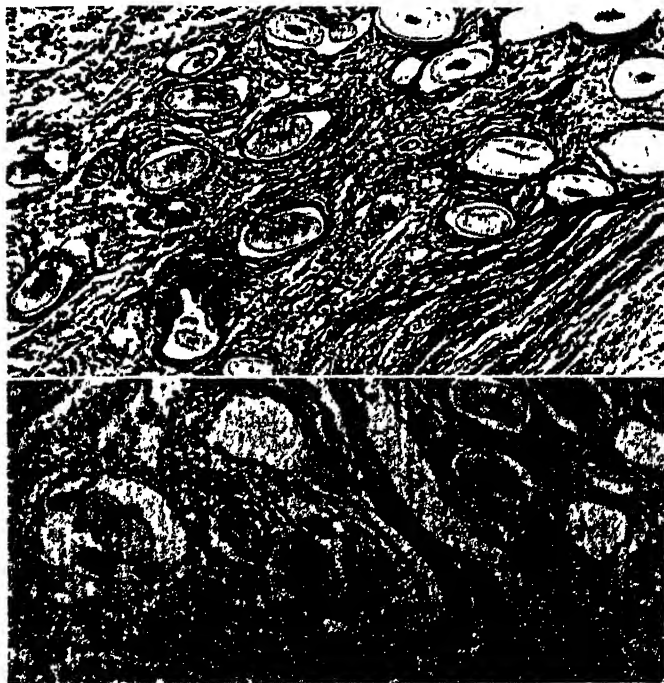


Fig. 225.—Pilonidal sinus. Note the shafts of hairs, some of which have foreign body giant cells around them, and the infiltration of chronic inflammatory cells.

Intestinal Obstruction

Complete obstruction to the passage of intestinal contents, either by a mechanical obstruction of the lumen (dynamic obstruction) or by a paralysis of the bowel wall (adynamic or paralytic obstruction) will bring about death in a relatively short period of time unless relieved. Such complete obstructions may be called acute, to distinguish them

from the partial mechanical obstructions of bowel lumen, which are compatible with life for long periods and hence are termed chronic obstructions.

The **chronic**, partial, mechanical obstruction of the intestine may be caused by a large variety of conditions, such as tumors in the bowel or pressing on it from the outside, adhesive or fibrous bands, impacted feces, etc. Above the point of obstruction the bowel is distended and there is hypertrophy of the muscular wall. There is, of course, danger that the obstruction may become complete and acute at any time.

An **acute** obstruction may be a simple mechanical obstruction, or there may be an associated interference with the blood and nerve supply of the intestine, in which case it is said to be strangulated. Interference with the blood supply to a segment of intestine, as in thrombosis of mesenteric vessels, results in a paralytic obstruction (paralytic ileus), although there may be no mechanical blockage. Obstructions with strangulation occur in hernias, and as a result of volvulus (twisting) or intussusception. Necrosis or infarction of the bowel wall occurs unless the blood supply is promptly restored. The involved portion of intestine becomes congested, edematous, hemorrhagic, and finally gangrenous. Ulcerations occur in and above obstructed portions of intestine (stercoral ulcers).

The actual cause of death in intestinal obstruction has been a matter of much study and debate. The effects vary depending upon the site and type of obstruction. High up in the intestinal tract, obstruction causes excessive vomiting with dehydration and chemical disturbances due to great loss of water and chlorides. In experimental obstructions life can be greatly prolonged simply by replacing these substances. In low intestinal obstructions, dehydration and electrolyte loss may or may not be very marked, and death appears to be due rather to the absorption of toxic substances. The exact nature of the toxic material is not clear. Part of the toxicity appears to be caused by histamine or a related substance, though multiple toxins probably are involved. The toxicity may be due to bacterial action on injured intestinal tissue.

Hernia.—An abdominal hernia is an abnormal protrusion of abdominal viscera outside the usual confines of the abdominal wall. Such protrusion may be through the inguinal canal, femoral canal, at the umbilicus, through a weak scar of an abdominal wound (ventral hernia), or through the diaphragm. Internal hernias are protrusions into intra-abdominal pouches.

A hernia becomes strangulated when there is a tight constriction of the loop of bowel at the neck of the sac. The constriction first compresses veins, in which the pressure is low, causing congestion and swelling of the herniated loop. This in turn increases the constriction until eventually the arterial supply is cut off as well, and the involved tissue soon becomes gangrenous.



Fig. 226.—Congenital diaphragmatic hernia. Note the stomach and loops of bowel in the left thoracic cavity. The diaphragm is held in the forceps.

DIAPHRAGMATIC HERNIA.—Herniation through the diaphragm may be congenital, i.e., due to abnormality of development, or may be acquired, as the result of trauma or wounds of the diaphragm.^{35, 36}

Congenital Hernia is quite frequently encountered in newborn or young children. It is about ten times more frequent on the left side. The hernia may be true, with existence of a hernial sac composed of peritoneum and pleura. More commonly the hernia is false, no hernial sac existing as the pleura and peritoneum are absent over the opening. Congenital false hernia is due to abnormal persistence of the

pleuroperitoneal canal, which connects the primitive pleural region with the abdominal region and normally becomes covered by a membrane about the seventh or eighth week of fetal life. There is usually associated an excessive mobility of the intestinal tract due to abnormal attachment of mesenteries.

Herniation may also occur through the esophageal hiatus. Other types of intra-abdominal hernias may occur, most commonly in or about the paraduodenal fossae, into the transverse mesocolon, or through the foramen of Winslow.³⁷

Volvulus.—Volvulus is a twisting or rotation of a loop of bowel, which, by its occlusion of blood vessels, may result in strangulation. The coil of intestine becomes obstructed and gangrenous.

Intussusception.—The invagination or passage of one portion of intestine into another segment is known as intussusception. The invaginated part tends to be carried along by peristaltic activity, dragging with it mesentery and blood vessels, which eventually become obstructed, so that there occurs congestion, edema, hemorrhage, inflammation, and adhesions. These changes may make reduction very difficult. Necrosis of the invaginated segment eventually develops. The condition is more common in young children, usually beginning in the ileocecal region. Sometimes polyps or other tumors of the intestine are dragged along by peristalsis and start an intussusception. Multiple small intussusceptions of the small bowel are common at autopsy. They are due to irregular intestinal contractions at the time of death, and being without inflammatory changes, are easily reduced.

Congenital Megacolon.—Megacolon, or Hirschsprung's disease, is a marked dilatation of the large intestine, usually throughout its entire length, with hypertrophy of the muscle fibers. The condition is congenital. Its exact etiology is unknown, though imbalance of nerve supply to the colon and sphincters has been postulated. The distended bowel produces considerable abdominal enlargement, and fecal evacuations occur only after abnormally long intervals.

Intestinal Lipodystrophy (Whipple's Disease)

Rare cases have been described in which there appears to be a disturbance of fat excretion and reabsorption from the intestines. Fatty diarrhea, accompanied by chylous ascites, a slight hypochromic anemia, and progressive emaciation proceeds to a fatal ending. The mucosa of the small intestine

shows dilated lymphatics; mesenteric lymph nodes are enlarged, have lost their normal architecture, and show dilated spaces and sinuses filled with amorphous fat or large foamy macrophages and some multinucleated giant cells.^{38, 39}

Melanosis Coli

Melanosis coli is a brown or black discoloration of the mucosa of the large intestine due to a melanin-like pigment held in large mononuclear cells. The pigment may also be found in the submucosa, and sometimes in mesenteric lymph nodes. Stasis of intestinal contents due to constipation or chronic obstruction is believed to promote absorption of protein disintegration products which then are converted into pigment by a tyrosinase-like ferment.

Tumors of Small Intestine

Tumors are uncommon in the small intestine. Various benign tumors, such as fibromas, myomas, and lipomas may involve the small bowel, but carcinoma is very rare. Lymphosarcoma may involve ileum as well as the region of the cecum or ascending colon.

Carcinoid Tumors.—Carcinoids are tumors which are carcinoma-like histologically, though benign or of very low malignancy. They are quite common in the appendix, less frequent in other parts of the intestine. They appear as small tumors in the mucosa and submucosa, of distinct yellowish color due to a high lipid content. In the appendix they are usually near the tip and may form an annular thickening which encircles the lumen. Microscopically they consist of clumps or masses of spheroidal cells with distinct nuclei but ill-defined cell borders. No glands are seen, though there may be some simulation of rosette formation. Mitoses are rare. There are granules in cytoplasm which stain with chrome and silver salts (hence sometimes they are termed chromaffinomas or argentaffinomas).

These tumors are believed to arise from Kultschitsky cells, which are argentaffine and chromaffine cells found at the base of Lieberkühn's glands, and common about the terminal ileum and appendix. The carcinoids of the appendix are almost wholly benign. Those in the small intestine may have a limited degree of malignancy and show local invasion and metastasis to lymph nodes. Carcinoids of the appendix must be distinguished from the rare true adenocarcinoma of the appendix by: (1) situation in the distal rather than the proximal part of the appendix, (2) the distinct yellow color;

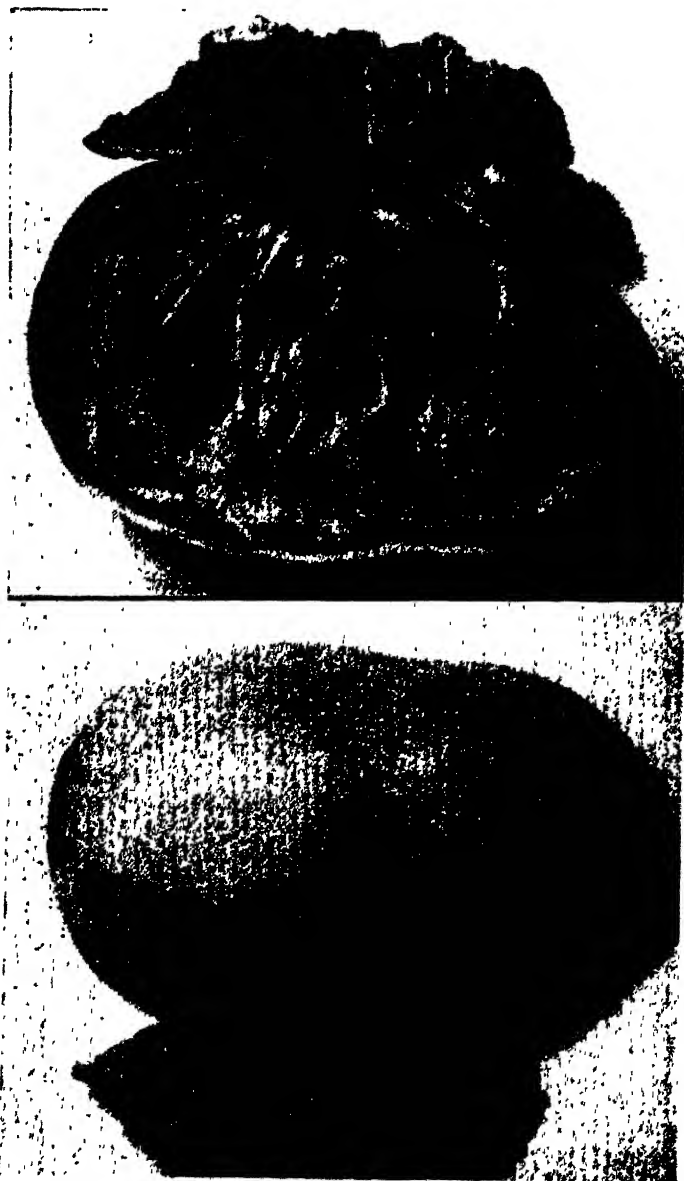


Fig. 227.—Myoma of ileum. (From South. M. J. 27: 386, 1934.)

(3) argentaffine and chromaffine granules in the cytoplasm; (4) lack or paucity of metastases; and (5) absence of glandular arrangement.

Tumors of the Colon and Rectum

Unlike the small bowel, the colon and rectum are common and important sites of carcinoma. The incidence is greatest in the sigmoid and rectum (55 per cent to 70 per cent), in the transverse colon and flexures (20 per cent), and in cecum and ascending colon (25 per cent). They are frequently preceded by benign adenomas or adenomatous polyps, which undergo malignant change. The tumors vary in rate of growth and degree of malignancy, but in many cases metastatic spread is late, and cure is possible by excision. Grading is helpful in prognosis. The age of greatest incidence is after fifty years, but younger ages are not exempt. Carcinoma of the rectum is slightly more frequent in males, and carcinoma of the colon is more frequent in females.

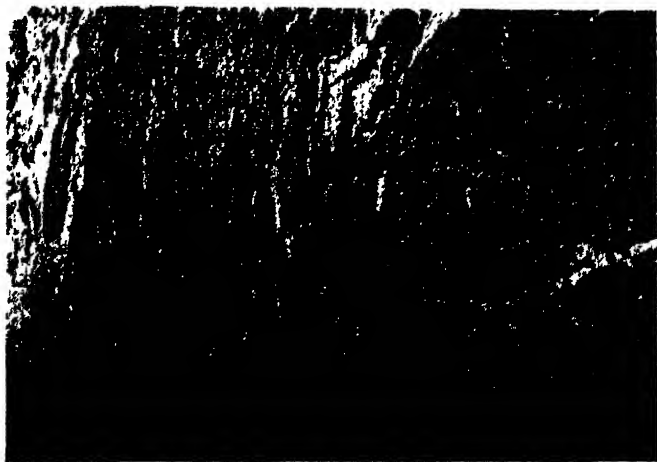


Fig. 228.—Carcinoid tumor of the appendix. The muscular layers of the appendiceal wall are seen on the left.

Adenoma and Polyposis.—Polyposis of the colon and rectum is common and is a well-established precancerous lesion.^{42, 43} Most of these (60 per cent or more) occur in the descending colon, sigmoid, and rectum, i.e., the same areas in which carcinoma is most frequent. The polyps are true

adenomatous tumors, to be distinguished from the inflammatory and hyperplastic areas of mucosa which simulate them in chronic dysentery and ulcerative colitis. There are two types of polypoid disease of the intestine: (1) Diffuse polyposis, in which large numbers of polyps involve the colon and rectum, and (2) localized or solitary polyposis, in which there are only one or a few polyps present. A definite hereditary factor is important in etiology. About 15 to 20 per cent of carcinomas of the bowel arise from these benign tumors. All stages in the change from normal mucosa to adenocarcinoma have been studied. About 50 per cent of all polyps are believed to undergo malignant change eventually.

Differentiation of benign polyps from those which have become malignant may be difficult. Lesions fixed to the mucous membrane by a broad base are more apt to be malignant than those with a pedicle. Tendency to ulceration is greater in the malignant polyps. Since malignant change can occur in any part of a polyp, sections from various portions must be examined before malignancy can be ruled out. Sections from the base and from the tip are particularly apt to show malignancy. The important criteria of malignancy are (1) invasion of underlying tissue (muscularis mucosa) or of lymphatics or blood vessels; (2) anaplasia of the epithelial cells; and (3) disorderly arrangement of glands.

Less common benign tumors of the large intestine are lipomas, leiomyomas, and carcinoids.⁴⁷

Carcinoma of Colon and Rectum.—

GROSS FEATURES.—The two main gross types are: (1) Annular and constricting and (2) papillary. The **annular constricting** type is often ulcerative. It grows around the bowel, thickening and contracting the wall and narrowing and obstructing the lumen. The **papillary** variety grows as a bulky mass projecting into the bowel lumen, thus giving rise to symptoms of obstruction. Necrosis and infection of the tumor mass and inflammatory lymphadenitis are common with this type.

HISTOLOGIC FEATURES.—Histologically, the tumors nearly always show some tendency to gland formation and hence may be termed adenocarcinoma. When this tendency is slight, the tumor cells form solid masses with scanty alveolar formation, and hence the tumor is of a medullary type. Stroma is often scanty or moderate in amount, but it may be so abundant that the tumor is scirrhus. Mucinous degeneration is found in about 5 per cent. This may be a mucoid change in individ-



Plate X.—Carcinoma of the rectum. (Courtesy Commander Clark E. Brown, M.C., USNR.)

ual cells, so that they have a signet ring appearance, or the mucoid material may be formed by the tumor alveoli, with mucinous deposition in a considerable area, in which but few tumor cells are evident.



Fig. 229.—Adenocarcinoma of sigmoid colon. The tumor encircles the bowel and constricts the lumen. Note the dilatation of the colon proximal to the region of chronic obstruction. (Courtesy Dr. H. C. Schmeisser.)

GRADING.—Classification according to degree of malignancy is important for prognostic and therapeutic purposes. There are two main methods of grading, Broders'⁴⁴ and Dukes',⁴⁵ and these methods are combined⁴⁶ for greatest effectiveness. The histologic method of Broders is based on the criteria of invasiveness, glandular arrangement, nuclear polarity, and

frequency of mitosis and indicates rate of growth of the tumor. Grinnel used these criteria for three grades of malignancy. Grade I is characterized by well-differentiated, compact glandular structure, nuclei of cells close to basal portion, little tendency to invasion of surrounding tissue, and infrequent mitoses. These tumors most nearly resemble adenomas and are sometimes termed "malignant adenomas." Grade II tumors have glandular arrangement preserved but irregular, nuclei in



Fig. 230.—Adenocarcinoma of cecum. The papillary tumor is projecting into the lumen. (Courtesy Dr. H. C. Schmeisser.)

variable positions, a greater invasive tendency, and more frequent mitoses. In Grade III the glandular structure is almost completely gone, cells grow in solid masses, the cell polarity is lost, invasion is irregular, and mitoses are numerous.

The mucoid carcinoma of signet ring type tends to be of high malignancy, in Grade II or III, while those not of the signet ring type are of lower malignancy, Grade I or II.

Dukes' method of classification is based on the degree of spread. In group A are placed the carcinomas which have not spread through the rectal wall, in group B, those which have penetrated the rectal wall but have not invaded the adjacent lymphatics, and in group C, those which have invaded the local lymphatics.



Fig. 231.—Carcinoma of rectum. The tumor has invaded the vaginal wall with production of a rectovaginal fistula. (Courtesy Dr. H. C. Schmeisser.)

In any large group of cases, there will be a fairly close correspondence in results of the two methods, but a combination of the two results in most accurate prognosis.

SPREAD AND METASTASIS.—Spread tends to be earlier in the flat, sessile growths than in the papillary type. It occurs by growth laterally around the bowel and outward through the wall. Local lymphatics then become affected. From a rectal cancer, this lymphatic involvement may be downward, lateralward, or frequently upward along the superior hemorrhoidal



Fig. 232.—Adenocarcinoma of rectum, with perforation. (Courtesy Dr. H. C. Schmeisser.)

vessels by way of the retrorectal lymph nodes to the nodes of the pelvic mesocolon. Spread by blood stream most commonly produces metastasis in the liver. Next to liver and regional lymph nodes, peritoneum and lungs are the most frequent sites of metastasis.

EFFECTS.—The disturbances produced by carcinoma in the colon and rectum depend upon the type of growth. Because the symptoms are often slight until a late stage, the condition must be kept in mind and investigation made on the least suspicion. Ulceration is usually accompanied by slight bleeding,

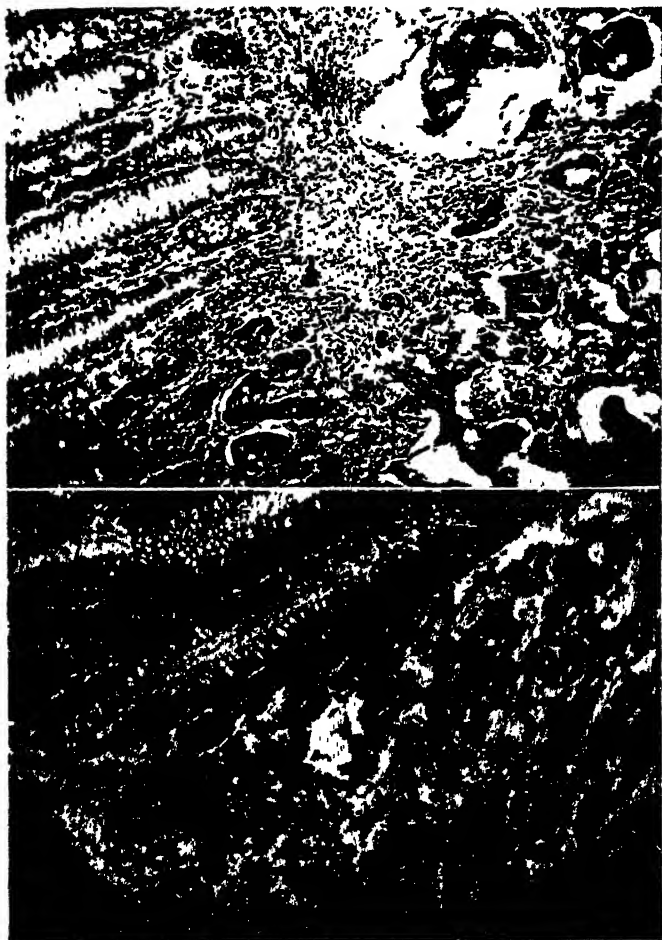


Fig. 233.—Adenocarcinoma of rectum. The edge of the tumor is shown in each figure, with the transition from normal to malignant epithelium. In the upper figure note the invasion of the submucosa, and the mucoid character in some areas.

so that blood is detectable in the stools. Chronic obstruction is often a late development, usually in the annular stenosing type of carcinoma. The bowel above the obstruction is dilated.



Fig. 234.—Carcinoma of rectum. The edge of the tumor is shown with normal mucosa on the left.



Fig. 235.—Mucoid carcinoma, metastasis in a lymph node.

PERITONEUM

The peritoneum is a closed sac in the male, but in the female communicates with the genital tract by openings at the ends of the Fallopian tubes. The smooth, shiny peritoneal lining is composed of flattened mesothelial cells, beneath which are a basement membrane and a small amount of connective tissue containing abundant blood vessels and lym-

phatics. The total surface area is very large, and through the peritoneum there is ready absorption, with equal facility in all parts. The omentum actively functions to wall off inflamed areas and to retard the spread of peritonitis. Inflammation is the most important lesion of the peritoneum. Ascites is the accumulation of excessive fluid in the peritoneal cavity. Primary tumor (mesothelioma) of the peritoneum is rare, but metastatic growths involving peritoneum are common. Mesotheliomas may have epithelium-like structures, but do not secrete mucin.

Peritonitis

Infection of the peritoneum may result by spread (1) from a ruptured viscus (e.g., perforated peptic ulcer or gangrenous appendix), (2) through an injured but unruptured bowel wall (e.g., in infarct of bowel), (3) from or by way of the internal genital organs (e.g., in puerperal endometritis, and primary pneumococcal peritonitis), or rarely (4) through the blood stream. The peritoneal infection may be walled off so as to be limited to a localized area, as in periappendiceal abscess or subphrenic abscess, or there may be generalized involvement. Death may be due to absorption of toxins, or to paralytic obstruction of a portion of intestine.

Acute peritonitis has been described as occurring in hyperemic, exudative, and plastic stages. These changes may be found locally or diffusely. In the hyperemic stage one sees marked dilatation and congestion of peritoneal vessels, giving the peritoneal surfaces a pinkish-blue color. This stage occurs early, probably within an hour after the perforation of an ulcer. It is rapidly followed by the exudative stage in which inflammatory cells and fibrin accumulate on the surfaces, and there is an increase in the amount of fluid in the peritoneal sac. In the plastic stage the exudate forms adhesions walling off the affected region or joining peritoneal surfaces. Organization or fibrosis may occur.

Fecal peritonitis is due to colon bacilli, which are common causative organisms in peritonitis. There is usually an abundant purulent exudate, which may have a fecal odor. **Streptococcal peritonitis** is often a fulminating infection, in which only a thin, serous exudate is found. It is one of the most serious types of puerperal infection. **Gonococcal peritonitis** is usually localized to the pelvis, having origin from an infected fallopian tube. It tends to become chronic and forms fibrous adhesions. **Pneumococcal peritonitis** may be primary in female children, the organisms reaching the peritoneum

through the fallopian tubes, or it may be secondary to pneumococcal infection in the lung or elsewhere. It is a common complication of the nephrotic syndrome in children.

Tuberculous peritonitis commonly results from local spread of the infection from the fallopian tube, intestine, or a mesenteric lymph node, but hematogenous infection from distant sources may occur. Tiny tubercles may fleck all peritoneal



Fig. 236.—Tuberculous peritonitis. The viscera are bound together by dense tuberculous exudate and granulation tissue. (Courtesy Dr. H. C. Schmeisser.)

surfaces. They appear as yellowish opaque spots surrounded by a reddish zone. The exudate may be very abundant and serous, so that a large amount of fluid accumulates in the peritoneal cavity. This is the moist form. A dry or plastic type also occurs, characterized by matting together of abdominal viscera by firm adhesions or by a dense granulomatous tissue.

Various rare types of peritonitis also occur, such as the rheumatic and actinomycotic forms.

Ascites

In ascites (edema of the peritoneal cavity) very large amounts of transudate may accumulate. It is seen in conditions in which edema is generalized, as in congestive heart failure, nutritional edema, nephritis and in obstructions to the portal circulation, as in cirrhosis of the liver. The watery fluid has a low specific gravity (usually less than 1.015), and low protein content (less than 2 or 3 per cent).

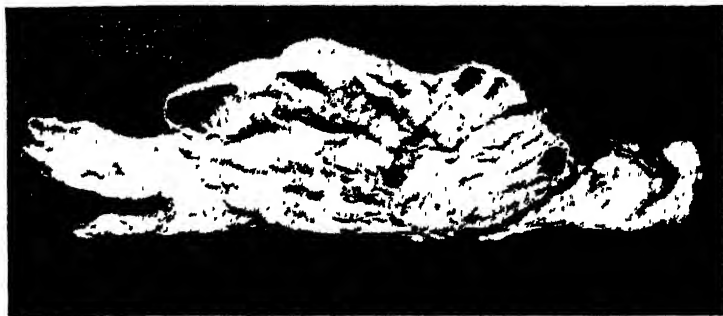


Fig. 237.—Tuberculous peritonitis, plastic (dry) type. Section through the intestinal mass seen in Fig. 236. (Courtesy Dr. H. C. Schmeisser.)

Fluid accumulation in the abdomen also may be an exudate due to inflammation, as in the moist form of tuberculous peritonitis. In such cases the fluid had a higher cellular and protein content, and higher specific gravity. Tumor metastasis to the peritoneum also may be associated with abundant fluid, particularly ovarian cystadenocarcinomas. It is often possible to identify tumor cells in the centrifuged sediment of such fluid.

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CHAPTER XX

ENDOCRINE GLANDS

THE PITUITARY GLAND (HYPOPHYSIS)

Structure and Function

The pituitary is a small endocrine structure situated in the sella turcica. Its main divisions are into anterior and posterior lobes. At the posterior part of the anterior lobe is the pars intermedia, though in man this has no distinct histologic separation from the anterior lobe. The important anterior lobe arises from Rathke's pouch (craniopharyngeal duct) an evagination of the roof of the posterior nasopharynx. From there the cells migrate upward to reach their final position in the sella turcica. Small portions of pituitary tissue may be left along this course and give rise to epithelial tumors (Rathke's pouch tumors), or simply remain as small remnants of pituitary tissue. Such ectopic nests of pituitary tissue are most often found in the pharyngeal mucosa (pharyngeal pituitary gland) or in the body of the sphenoid bone. The posterior lobe develops as a down-growth from the floor of the third ventricle and hence is of nervous origin. The posterior lobe becomes enveloped anteriorly by the anterior lobe.

The anterior lobe contains three main types of cells. About 50 per cent are **chromophobe** cells, which have a cytoplasm devoid of specific granulation. The chromophobes give rise to the other two types, **acidophiles** (40 per cent) and **basophiles** (10 per cent) by the accumulation of specific cytoplasmic granules which respectively stain red with acid dyes and blue with basic dyes. In castrated or aged individuals there is a vacuolation of the basophiles, and in certain castrated animals the vacuolation is sufficient to produce a distinctive "signet ring" type of cell. Also during pregnancy there is in the hypophysis a somewhat distinctive type of cell, which is apparently a specialized acidophile of high secretory activity.¹

The anterior lobe elaborates a number of principles, though it is uncertain how many of these may be distinct hormones. These may be grouped as: (1) a growth-promoting principle; (2) principles stimulating other glands,

such as thyroid, parathyroid, adrenals, gonads, etc.; and (3) principles regulating metabolism of certain substances, such as fat, water, and nitrogen. It seems established that the growth-promoting hormone is elaborated by the acidophiles. Regarding the site of formation of the other hormones, there is more uncertainty. The chromophobes are apparently without secretory function.

The posterior lobe is composed of neuroglial cells (pituitocytes), nerve fibers, and some hyaline bodies. This portion of the pituitary is connected by nerve tracts with nuclei of the floor of the third ventricle, which perhaps control its activity. The function of the posterior lobe is a matter of debate, but it probably influences (1) water balance, by control of urine flow; (2) carbohydrate metabolism; and (3) the onset of parturition. An extract of the posterior lobe, pituitrin, contains two powerful fractions: pitocin, which stimulates uterine contractions, and vasopressin, which constricts arterioles. Whether these substances are actually formed in the posterior lobe or are from the pars intermedia is still in dispute.

The *pars intermedia* contains the same cells as the anterior lobe, though basophiles are more numerous. A few small cystic spaces containing pink staining colloid-like material are usually present at the junction with the posterior lobe. A few basophiles which are sometimes found in the posterior lobe are probably derived from the *pars intermedia*.

Diseases of the Pituitary

Pathologic changes in the pituitary may be: (1) adenomas or hyperplasias, which may result in pituitary hyperfunction, pressure effects, or both; (2) destructive lesions, as a result of inflammation, thrombosis, embolism, atrophy, or pressure from adjacent tumors. These changes are associated with hypofunction of the gland.

PITUITARY ADENOMAS

Chromophobe Adenoma.—Chromophobe adenoma is the most common type of pituitary tumor. It varies from less than a millimeter to several centimeters in diameter. Since the chromophobes elaborate no specific hormone, the effects are due simply to pressure of the expanding growth. Such pressure effects are on the surrounding glandular tissue of the pituitary, the bony and membranous walls of the sella

turcica, and the optic chiasm. Pressure on the surrounding normal glandular tissue may produce various symptoms of hypopituitarism.

Acidophile Adenoma.—Tumors composed predominantly of acidophiles cause clinical syndromes prominently featured by overproduction of growth hormone. If the adenoma develops within the growing period before ossification is complete, **giantism** results; if after bone growth is completed, **acromegaly** is produced. Acromegaly is characterized by overgrowth and thickening of bones, conspicuous in the skull, face, mandible, and peripheral portions of extremities. Overgrowth of viscera and fibrous hyperplasia of skin and subcutaneous tissue also occur. Other disturbances usually present are sexual disorders of impotence or amenorrhea, and glycosuria. Eventually pressure effects result from continued growth of the adenoma. The pressure first may be on other portions of the gland, giving rise to evidence of hypopituitarism, then on suprasellar regions where pressure on the optic chiasm or optic nerves produces visual disturbances.

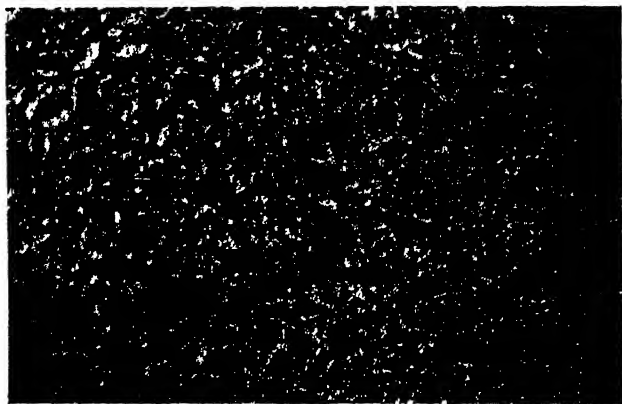


Fig. 238.—Chromophobe adenoma of pituitary.

Basophile Adenoma.—The least common type of pituitary adenoma is composed of basophilic cells. It is associated with a clinical condition, known as "**Cushing's syndrome**" or "pituitary basophilism." The clinical features are obesity (confined to the face, neck, and trunk), hypertension, polycythemia, a dusky cyanotic tinge of the skin, purplish striae on the breast and abdomen, hirsutism and

sexual disturbances. In 1932 Cushing pointed to the frequent association of this syndrome with a pituitary basophilic adenoma or hyperplasia. Later studies have shown that the association is not constant. Similar or identical clinical syndromes may occur with an adrenal cortical tumor or hyperplasia, or more rarely with a thymic tumor or atrophy of the paraventricular nuclei of the hypothalamus, probably secondary to a slight internal hydrocephalus.² However, the clinical syndrome does seem to be quite constantly associated with a degenerative change in the pituitary basophiles. This change, consisting of replacement of the cytoplasmic basophilic substance by a hyaline material, has been described by Crooke³ and verified by others.⁴ Much evidence indicates a close association of the pituitary and hypothalamic centers.⁶ High values in the assay of urinary 17-ketosteroids suggest the presence of an adrenal tumor.⁸

THE PITUITARY IN DISEASES OF OTHER ORGANS

Cellular changes in the anterior pituitary in association with various other conditions are less well established.¹ Basophiles have been reported to be numerically increased in hypertension, glomerulonephritis, and obesity. Their number is greatly reduced in Addison's disease. Hydatidiform mole and chorionepithelioma produce changes in the pituitary similar to those in pregnancy.

HYPOPITUITARISM

Injuries or destructive lesions of the pituitary are not frequent. Pressure effects may be produced by tumors in or around the sella. Syphilis may cause a diffuse fibrosis of the pituitary. Septicemia and embolism occasionally affect the hypophysis. The most common type of severe injury is a necrosis which occurs after childbirth, particularly in those cases in which there have been severe post-partum hemorrhage and collapse. The necrotic area undergoes fibrosis, and if it is extensive, hypopituitarism results.

Simmonds' Disease.—Simmonds' disease is the result of severe hypopituitarism in the adult.⁹ The condition is uncommon in men, as most cases appear to be the late effects of a post-partum necrosis of the pituitary. The condition is characterized by severe cachexia, loss of sexual function, low metabolic rate, weakness, loss of hair, pigmentation of the skin, and premature senility. Not only is there atrophy or destruction of the anterior lobe of the pituitary but also

fibrosis or atrophy of the thyroid, parathyroids, adrenals, ovaries, and endometrium. Low blood pressure, hypoglycemia, and evidence of myxedema are usually present. Cachexia is not invariably present and is not a necessary feature of hypopituitarism. The cachexia is dependent mainly on loss of appetite and subsequent undernutrition. An unrelated condition, **anorexia nervosa**, is characterized by marked cachexia due to undernutrition. It has many of the clinical features of Simmonds' disease, with which it is often confused, but changes in the pituitary and other endocrine glands are lacking.

Progeria.—Progeria is the childhood equivalent of Simmonds' disease. Here the hypopituitarism results in dwarfism and the appearance of senility.

Other Pituitary Syndromes.—Various other clinical syndromes are related to disturbances of pituitary function. They are less clear-cut and their pathologic basis is less definite. **Dystrophia adiposogenitalis** (Fröhlich's syndrome) is characterized by adiposity of the trunk and a feminine configuration. It is probably a hypopituitarism and often related to pressure on the pituitary by tumors. **Dwarfism** may be attributable to hypopituitarism. Failure of sexual development is a common accompaniment. There may be marked obesity (Brissaud type) or no obesity (Lorain type).

The **Laurence-Moon-Biedl Syndrome** is characterized by obesity, hypogenitalism, polydactylism, pigmentary retinal changes, and failure of proper mental development. While having a genetic basis, various endocrine changes have been found, including increase of pituitary basophiles.¹³ Also **mongolism**, a prenatal developmental disorder, shows evidence of pituitary involvement with secondary changes in the thyroid, adrenals, and gonads.¹⁴

Hyperostosis Frontalis Interna (metabolic craniopathy) is a familial condition in which irregular thickening of the skull, most often in the frontal region, is associated with metabolic, endocrine, and neuropsychiatric manifestations. It occurs almost entirely in women, usually beyond the age of 35, and is often associated with headache, "pituitary" obesity, amenorrhea, hirsutism, and hypertension. It has been suggested that displacement of the brain by the bony thickening strains the pituitary stalk, providing a basis for the various changes which could be of pituitary or hypothalamic origin, although there may be no demonstrable lesion of the pituitary.¹⁵

Diabetes Insipidus.—Diabetes insipidus is characterized by excessive output of urine of low specific gravity and without sugar. Excessive thirst and intake of fluid accompany the condition. It is related to disturbance of the posterior lobe of the pituitary, or to injury of the hypothalamus. Secretion of an antidiuretic hormone by the hypophysis is apparently under nervous control of the hypothalamus. Hence either hypothalamic or pituitary injury may result in diabetes insipidus.

RATHKE'S POUCH TUMORS

Remnants of Rathke's pouch or the craniopharyngeal duct may give rise to cystic tumors (craniopharyngiomas, suprasellar cysts). Being composed of epithelium derived from the mouth cavity, the tumors consist of a squamous type of epithelium. This epithelium resembles the ameloblasts of the developing enamel organ, and consequently the tumor is often strikingly similar in its microscopic appearance to the adamantinoma (ameloblastoma) which arises in the jaw (see page 456). A few cystic tumors of the pituitary have been lined by ciliated epithelium.

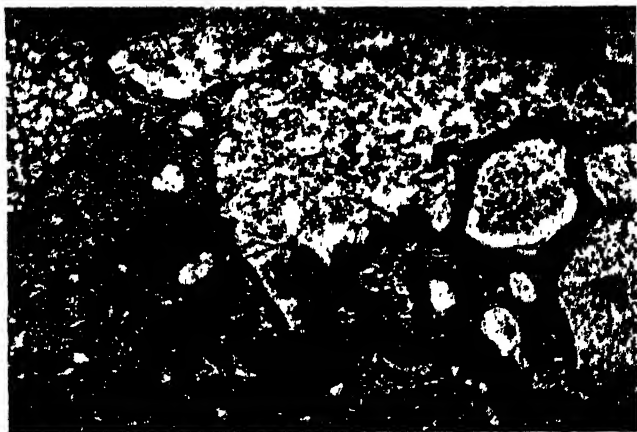


Fig. 239.—Cystic craniopharyngioma. (Adamantinoma of hypophyseal duct.)

Many of the craniopharyngeal tumors develop from the region of the hypophyseal stalk, are cystic, and lie above the diaphragm of the sella. Hence the term of suprasellar cyst is common. Being of congenital origin, they may be found

in early age periods, often before fifteen years. They are benign growths, their serious effects being due to pressure. Various types of dyspituitarism and stunting of growth may result.¹²

THE THYROID GLAND

Development, Structure, and Function

The thyroid develops as a downgrowth from the region of the primitive pharynx. A mass forms at the base of the tongue and extends downward as a long tube, the thyroglossal duct, its final position being in front of the trachea, and thyroid cartilage. The upper end of the thyroglossal duct is marked by a small depression at the root of the tongue, the foramen cecum. Normally the duct is obliterated during fetal life. Failure of the complete downgrowth and disappearance of this tissue leave aberrant thyroid tissue at the base of the tongue (lingual thyroid) or in the neck anywhere along the course of the thyroglossal duct. These nests of thyroid tissue may give rise to midline (thyroglossal duct) cysts, which must be distinguished from the lateral (branchial cleft) cysts of the neck.

The units of thyroid tissue are glandular vesicles or acini. They are lined by a layer of epithelial cells, whose function is to remove iodine from the blood and elaborate it into an active hormone. A constituent of this hormone, thyroxine, has been identified and synthesized. Factors which influence the activity of the thyroid include the amount of iodine available for synthesis, and the thyrotropic hormone of the pituitary. Material elaborated by the thyroid cells passes into the lumen of the vesicle where it is stored as a homogeneous material known as colloid. As necessary, the colloid is resorbed back through the thyroid cells and secreted into the blood stream. Cyclic activity of colloid formation and resorption occur. Colloid resorption appears to be brought about by the thyrotropic hormone of the pituitary. A deficiency of stored iodine from any cause promotes hyperplasia and enlargement of the thyroid.²¹

The thyroid controls the rate of general body metabolism. Its proper secretion is necessary for normal physical, sexual, and mental development and function. Abnormalities of thyroid function may be in the direction of deficiency (hypothyroidism) or excess (hyperthyroidism). Hypothyroidism gives rise to cretinism in infants and children and myxedema

in adults. Hyperthyroidism may occur in severe form with a diffuse enlargement of the thyroid (Graves' disease, exophthalmic goiter), or in a milder form in which the thyroid enlargement is nodular (toxic adenoma). The thyroid hormone acts to accelerate oxidation or rate of metabolism of cells or of the whole organism. The protein-bound iodine of the blood is an index of the amount of circulating thyroid hormone, and closely correlates with thyroid function in hyper- or hypothyroidism.

The histologic structure of the thyroid reflects its functional activity, so that a condition of under- or overactivity sometimes may be judged by microscopic examination. It must be borne in mind, however, that the activity of the normal thyroid tissue is cyclic, and that in diseased thyroids different portions of the gland may show different stages or degrees of activity.

The type of epithelium lining the follicles is the most important criterion of thyroid activity. Tall columnar epithelium resorbs hormone from the follicular lumen and discharges it into the blood stream; high cuboidal epithelium actively produces colloid; low cuboidal epithelium produces colloid slowly; low, flat epithelium is inactive. Hence the height of acinar epithelium acts as an index of functional activity, and probably also of the action of thyrotropic hormone of the pituitary.^{17, 18} Secretory activity is characterized by cellular hypertrophy with a change of resting low cuboidal epithelium to a columnar type. When activity becomes excessive, epithelial proliferation (hyperplasia) also occurs. Infoldings of the follicle wall result from the cellular increase and may be simply slight elevations or definite lace-like papillae. Increase in thyroid activity is also accompanied by changes in the mitochondria and Golgi apparatus, demonstrable only by special cytologic methods. The nature of the colloid content of the follicles may also indicate the degree of activity. Under conditions of glandular activity and active resorption into the circulation, the colloid is very pale staining and vacuolated, particularly about its periphery. Apparently this represents the transformation of the intrafollicular colloid into a thinner, more soluble form. Continued preponderance of resorptive activity over colloid formation eventually produces exhaustion of the gland. When iodine is administered to an individual with a hyperactive thyroid, colloid storage is promoted and for a time may predominate over resorption, with resulting clinical improvement. The im-

provement, however, is only temporary, since the tendency to excessive resorptive activity still exists, and more colloid has been made available.

The pituitary produces a thyroid-stimulating hormone, of protein nature, administration of which to animals has reproduced many of the changes seen in human hyperthyroidism (Graves' disease). It has been postulated that there exists normally a balance between the pituitary and the thyroid, any deficiency of the thyroid stimulating the pituitary to produce more of its thyrotropic hormone, and conversely any overadequate supply of thyroid hormone reducing the pituitary production of the thyroid-stimulating factor.¹⁹ Disturbances of this normal balance may be the basis of some cases of hyperthyroidism and hypothyroidism. The hyperplastic thyroid tissue of Graves' disease has been shown to inactivate the thyroid-stimulating hormone of the pituitary in greater amount than normal tissues, whereas tissue of nontoxic goiters has little or no inactivating effect on the thyrotropic hormone.²⁰

Goiter

The term goiter, or struma, refers to an enlargement of the thyroid gland. Such enlargement may be related to several different etiologic factors; it may be diffuse or nodular (adenomatous), and it may be associated with a deficient, normal, or excessive production of hormone. A large variety of classifications of goiter have served to confuse the subject unnecessarily. Five main types may be recognized:

1. Simple (colloid) goiter, which is endemic to certain regions and has its origin in iodine deficiency.

2. Diffuse goiter with hyperthyroidism (exophthalmic goiter, Graves' disease, Basedow's disease).

3. Nodular (adenomatous) goiter:

- a. with hyperthyroidism (toxic adenoma).

- b. with hypothyroidism (cretinism, myxedema)

4. Inflammatory goiter:

- a. Lymphadenoid goiter (struma lymphomatosa).

- b. Riedel's struma.

5. Neoplastic goiter:

- a. benign (adenoma).

- b. malignant (carcinoma).

It is probable that the nodular goiter with hyperthyroidism and the diffuse (exophthalmic) goiter are but variations or stages of a single disease, with no fundamental difference in their nature.

SIMPLE OR ENDEMIC GOITER

In certain regions of the world goiter is endemic and occurs with great frequency. Such regions are particularly about great mountain ranges, but in North America a goiter belt also occurs around the Great Lakes and St. Lawrence Valley. The thyroid enlargement is a response to insufficient iodine intake, due in these regions to deficiency in the soil and water. Bacterial contamination of water supplies may interfere with availability or absorption of iodine and give rise to goiter. Endemic goiter may be prevented by the addition to the diet of minute amounts of iodine, as by use of iodized salt. The condition occurs more commonly in females and is particularly apt to develop at a time when the thyroid is subjected to extra functional stress, as in adolescence or pregnancy.

Gross examination of simple goiters shows great variation in size. The whole gland may be involved diffusely or it may be nodular, with patchy "adenomatous" areas. Probably the enlargement is always diffuse in the beginning, but successive cycles of uneven hyperplasia and involution give rise to the nodularity. The cut surface of the gland has a highly translucent appearance due to the abundant colloid. Degenerative changes are often evident, particularly in the nodular type, and there may be hemorrhage, cyst formation, and calcification. Coarse, irregular connective tissue trabeculae separate the adenomatous nodules.

Microscopically, the goiter may be composed of large distended follicles, filled with abundant deeply staining colloid and lined by a low cubical or flattened inactive type of epithelium. Such a "colloid goiter" is in an involutionary phase and has been preceded by a stage of hyperplasia in response to the iodine deficiency. Subsequent flare-ups of hyperplasia, followed by involution and colloid accumulation, produce a nodular colloid goiter.

In some cases of simple goiter the gland is composed of small inactive follicles without excess colloid accumulation. This variety is termed by some the parenchymatous or micro-follicular type.

HYPERTHYROIDISM

Hyperthyroidism is the result of a hyperplastic overactive thyroid which secretes an excess of hormone into the circulation. It is possible that in some cases there may be production of an abnormal hormonal product rather than a simple quantitative excess. However, no proof of this has arisen, and

the quantitative concept appears at present to fit the facts best. Hyperthyroidism may be of all grades of severity; those cases having a diffuse thyroid hypertrophy and hyperplasia (exophthalmic goiter) being in general more serious than those with nodular thyroids. There appears to be no fundamental difference between the diffuse and the nodular hyperplastic goiters as far as the thyroid factor itself is concerned. Histologic changes of hypertrophy and hyperplasia within the thyroid indicate excessive secretory activity. The quantitative concept must be borne in mind, however, in any attempt at functional interpretation from a tissue section. In the diffuse goiter of Graves' disease such functional interpretation may be highly accurate. In nodular goiter there is great variation in activity in different portions of the gland and hence also in the microscopic picture. This precludes accuracy in any attempted estimation of function.

Diffuse Goiter With Hyperthyroidism.—Diffuse goiter with hyperthyroidism (exophthalmic goiter, Graves' disease) is the most acute and severe type of hyperthyroidism. It occurs particularly in adults of young and middle age. 'The incidence is sporadic and not limited to the "goiter belts." There is evidence that the condition is a constitutional nervous and hormonal imbalance. In this imbalance the hyperthyroidism is only one part, though often the predominant manifestation. The actual stimulus for the hyperactivity of the thyroid is probably an excess of the pituitary thyrotropic hormone. A generalized hyperplasia of lymphoid tissue is a common accompaniment.

While usually associated with diffuse goiter, the thyroid enlargement is often slight and does not necessarily parallel the severity of the clinical symptoms. Exophthalmos, or protrusion of the eyes, is an inconstant feature. It is apparently not a direct result of hyperthyroidism, and cannot be reproduced by thyroid extract. Exophthalmos has been produced experimentally by injection of pituitary extract containing thyrotropic hormone. Increased metabolic rate, tachycardia, and nervous excitability are prominent features more closely related to the thyroid hyperfunction. A negative iodine balance is present. The condition may develop slowly or suddenly and proceed through a course which may be rapid, or prolonged by a series of exacerbations and remissions. The end result is an exhausted condition of the gland with actual hypothyroidism. Cardiac damage usually occurs, often marked by disturbances of rhythm, such as auricular fibrillation.

The gross appearance of the thyroid gland is similar in all parts. Though it may not be much enlarged, it is highly vascular and has a characteristic meaty and firm consistency. The cut surface has a solid, firmly lobulated appearance, without the translucence imparted by a rich colloid content. By the promotion of colloid accumulation preoperative iodine administration may change the aspect to a glistening translucence not unlike that of the normal gland.



Fig. 240.—Diffuse goiter with hyperplasia (Graves' disease). (Courtesy Dr. H. C. Schmeisser.)

Microscopically, characteristic features of thyroid hyperactivity are evident throughout the gland. The epithelial cells of the follicles are tall and columnar, their nuclei closely packed and basal in position. Papillary epithelial proliferation with lace-like projections into follicular lumina is often marked. Hypertrophy of the Golgi apparatus is demonstrable by silver staining. New follicles with small lumina may be

formed. The colloid is decreased in amount, thin, pale, and vacuolated or scalloped around the edges. Accumulations of lymphocytes, often with distinct germinal centers, are frequently prominent. By itself the lymphoid hyperplasia is not good evidence of thyroid hyperfunction.



Fig. 241.—Hyperactive thyroid (Graves' disease). Note the tall epithelium lining the acini, and the vacuolation and scantiness of the colloid.

The preoperative administration of iodine usually causes a change in this picture before it is seen in the laboratory. The epithelium is changed to a cuboidal form, the acini becoming larger, with less infolding of epithelium and containing a more deeply stained colloid. This involutionary change is not diffuse and patchy areas still exhibit hyperplastic character. The lymphoid accumulations are not influenced by the iodine medication.

Cyanides and thiocyanates administered to experimental animals have produced goiters with marked hyperplasia of the thyroid tissue but hypothyroidism. Therapeutic use of thiocyanate in man occasionally has been complicated by a

similar effect, with production of a goiter due to marked hyperplasia of the gland, but accompanied by symptoms of hypothyroidism, a low basal metabolic rate, and low blood iodine. This effect of thiocyanate is preventable by administration of iodine, or can be relieved by giving thyroid.²⁸



Fig. 242.—Thyroid following thiouracil therapy. Note marked hyperplasia and almost complete absence of colloid.

Thiouracil and other thiourea derivatives have been found therapeutically effective in relieving hyperthyroidism. However, there may be an increase in size of the gland, which microscopically may show a very marked degree of hyperplasia and little colloid content. The effect in this case does not appear to be preventable by iodine. It is postulated that thiocyanate and thiouracil block at different points either the formation or the action of the thyroid hormone. Meanwhile the thyroid gland itself is increasingly stimulated to a "hyperplasia of frustration" by the unopposed pituitary thyrotropic hormone, or by a decrease of stored iodine within the gland. The extreme degrees of hyperplasia of thyroid tissue which may be seen as a result of thiouracil or thiocyanate therapy must be distinguished with care from neoplastic tumors of the thyroid.^{23, 24, 25}



Fig. 243.—Nodular (adenomatous) goiter. Areas of hemorrhage and degeneration are evident on the cut surface. (Courtesy Dr. H. C. Schmeisser.)

Various other organs may show changes in severe hyperthyroidism. Lymphoid hyperplasia is generalized, not simply in the thyroid itself. The thymus is often enlarged and even the blood may show a relative lymphocytosis. The heart shows few changes, despite the frequent occurrence of cardiac complications. There may be cardiac hypertrophy and some myocardial degeneration and fibrosis. Voluntary muscles, such as the quadriceps, also may show degenerative changes. Some skeletal decalcification is common. Exophthalmos is produced by edema of the fat in the orbital cavity and by a marked swelling, degeneration, and cellular infiltration of the extrinsic ocular muscles. Secondary ulceration of the cornea may complicate severe exophthalmos. The liver is affected by hyperthyroidism, and in severe cases may show fatty degeneration and necrosis. The adrenal glands also may be involved by degenerative and atrophic changes.

Nodular Goiter With Hyperthyroidism.—Hyperthyroidism with a nodular goiter (toxic adenoma) is probably fundamentally the same condition as Graves' disease, though some have maintained that production by the gland of an abnormal toxic product distinguishes the condition. The nodularity is the result of recurring cycles of hypertrophy and hyperplasia affecting the gland in irregular fashion. Because the hyperactivity may appear in a previously existent simple goiter, it is sometimes termed secondary Graves' disease. The condition tends to occur in later life, the degree of hyperthyroidism is milder, and exophthalmos is usually absent. Large nodular goiters may cause disturbance by pressure on surrounding structures, e.g., trachea.

Both the gross and microscopic appearance is extremely variable. The enlargement of the thyroid may be very marked and irregular. Areas of degeneration are often present. Nodular or adenomatous areas of varying size may show fibrosis around them. Their cut surface may be meaty and firm indicating hyperplasia, or soft and translucent, due to colloid storage. The appearance is often quite variable in different portions of the gland, both grossly and microscopically. Hence there is difficulty of evaluation in terms of function, which evidently depends upon the total balance of hyperplasia and involution.

HYPOTHYROIDISM

Insufficient function of the thyroid produces in early life the condition of cretinism, and in the adult, myxedema. While fundamentally the same, the clinical syndromes differ

because of the retardation and distortion of physical, sexual, and mental development in the childhood form.

Cretinism.—Cretinism occurs sporadically. It is due to a hypoplasia or failure of proper development of the thyroid. The thyroid may be absent, or consist of only a few glandular remnants set in connective tissue. Cretinism also commonly occurs in regions where goiter is endemic, as a result of thyroid deficiency in the mother. In this latter instance unsuccessful attempts at compensatory hyperplasia may produce a goiter of considerable size in the cretin. The thyroid tissue is mainly in a hypoplastic or involutionary state.

Skeletal growth is stunted and distorted, the skin is thick and coarse, hair is scanty, metabolism is depressed, and sexual and mental development are of low degree. Thyroid administration may be helpful if administered early enough, but it rarely produces complete restitution to normal development.

Myxedema.—Myxedema is the antithesis of Graves' disease. The general metabolism is low, heat tolerance is increased, and physical and mental activities are retarded. The skin becomes dry, coarse, and thickened by subcutaneous accumulation of a mucoid material. This results in the appearance of a non-pitting edema, particularly prominent on the face, neck, and hands, which feature has given origin to the term myxedema. The hair tends to become coarse and scanty. Loss of sexual desire and impotence or amenorrhea are common. The condition responds readily and effectively to thyroid administration.

Mild degrees of myxedema may follow operative removal of most of the thyroid gland or result from exhaustion of the gland following severe hyperthyroidism. Most cases are of unknown etiology. The thyroid tissue is atrophic and inactive, often displaying marked fibrosis. Vacuolization and hydropic degeneration of cardiac and skeletal muscle fibers have been noted.²⁷ A similar chromatropic degeneration in the media of the aorta leading to fatal rupture has been described in induced hypothyroidism.²⁸

INFLAMMATION OF THE THYROID

The thyroid appears quite resistant to most infections, so that inflammatory processes in the thyroid are uncommon. Direct spread may occur from neighboring tissues. However, two distinctive types of supposedly inflammatory conditions are termed lymphadenoid goiter and Riedel's struma.

Lymphadenoid Goiter.—Lymphadenoid goiter (Hashimoto's disease, struma lymphomatosa) is a condition in which excessive lymphoid tissue develops in the thyroid, often with prominent lymphoid follicles, and a crowding out and replacement of thyroid acini. The thyroid tissue

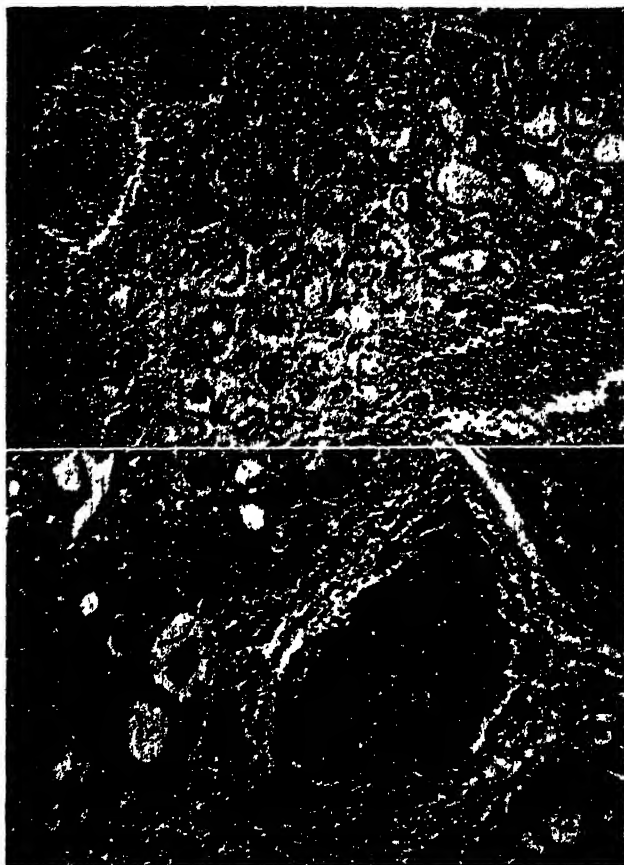


Fig. 244.—Early struma lymphomatosa (Hashimoto's disease).

is nodular, of uniformly firm consistency, and a white to yellowish-brown color. The occurrence may be at any age, but most cases seem to be in women over 40 years. Moderate diffuse enlargement of the thyroid is usual. Functional disturbance is usually not a prominent feature, but mild hypo-

thyroidism (myxedema) may be present in later stages. Slight relative lymphocytosis of the blood may be present.^{29, 30}

The inflammatory nature of the condition has often been in doubt. A lesser degree of lymphoid involvement is common in hyperfunctioning thyroids (e.g., exophthalmic goiter). Some consider lymphadenoid goiter a functional disturbance in which the basic cause is excess of thyrotropic hormone. Others have concluded that lymphadenoid goiter is but an early stage of Riedel's struma, and that slow progressive replacement by fibrous scar tissue will produce the hard goiter of this latter condition.

TABLE XV

DIFFERENTIAL FEATURES OF HASHIMOTO'S STRUMA LYMPHOMATOSA AND RIEDEL'S STRUMA (MODIFIED FROM JOLL²⁹)

HASHIMOTO'S STRUMA LYMPHOMATOSA	RIEDEL'S STRUMA
1. Occurs mainly in women from 45 to 60 years of age.	Occurs in men and women of younger average age.
2. Tendency to myxedema.	Little tendency to myxedema except after radical operations.
3. Diffusely involves all of thyroid, but no tissues around thyroid.	Often unilateral or involving only a portion of thyroid, and extends to extrathyroid structures.
4. Goiter may be large, but never very hard, and tends to be lobulated.	Goiter is small, intensely hard, and smooth.
5. Pressure effects seldom severe.	Pressure effects are the rule.
6. Diffuse lymphocytic infiltration, with prominent lymph follicles, and followed by fibrosis.	Dense fibrous scar tissue, absence of diffuse lymphocytic infiltration and lymph follicles, sometimes giant cells, extension to surrounding tissues.

Riedel's Struma.—Riedel's struma (woody thyroiditis) is characterized by a thyroid of very firm consistency. Its essence is a slow progressive replacement of thyroid tissue by dense scar tissue, and extension of the fibrous tissue to involve surrounding structures. It occurs at any age, but usually in adults, and almost as frequently in men as in women. It may be associated with mild hypothyroidism, and is easily confused clinically with carcinoma.

While extensive fibrosis is the essential microscopic feature, lymphoid accumulation is frequently prominent and forms occur which are transitional between lymphadenoid goiter and Riedel's struma. Multinucleated giant cells in the lesion may be mistaken for the giant cells of tuberculosis. Goetsch³¹ has suggested that the giant cells are formed

by fusion of follicular epithelial cells desquamated into the lumen. The etiology is unknown. It has been suggested that it may begin as a perithyroiditis which narrows or occludes

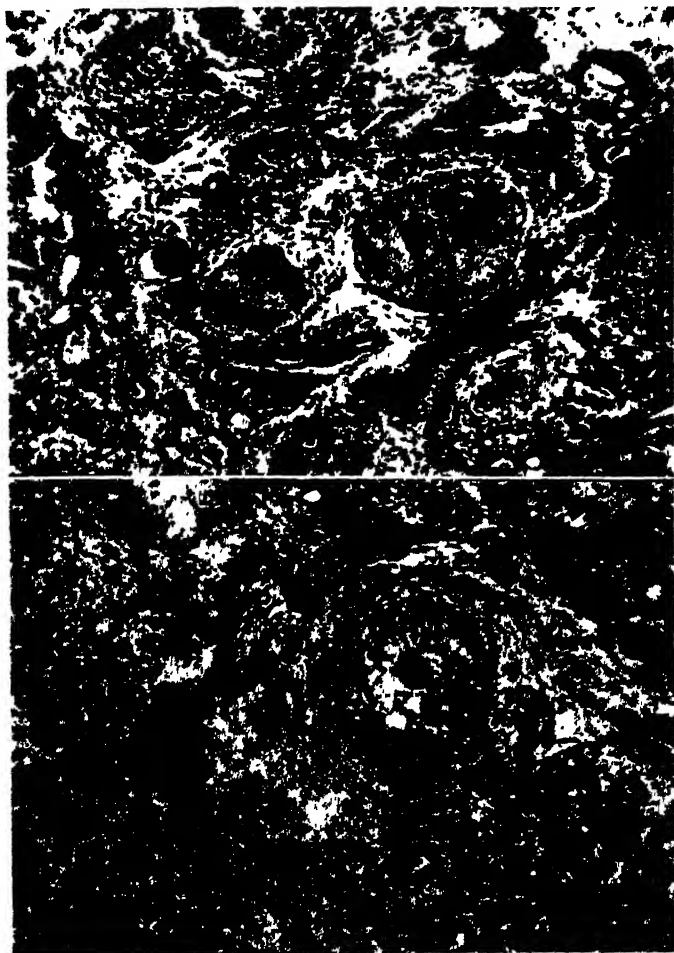


Fig. 245.—Riedel's struma: multinucleated giant cells, fibrosis, lymphocytes, and a few thyroid follicles.

blood vessels entering the gland.³² Extensive involvement of adjacent structures of the neck by the dense fibrous tissue makes surgical resection difficult.

Tumors of the Thyroid

The common neoplasms of the thyroid are adenomas and carcinomas. Most carcinomas of the thyroid are believed to originate in a benign adenoma.

Adenoma of the Thyroid.—The so-called “adenomas” of nodular goiters are not true tumors, but localized areas of hyperplasia or involution. Criteria for true thyroid adenomas are: (1) complete encapsulation, (2) homogeneous texture throughout, though degenerative changes may be present, (3) definite variation of the tissue of the adenoma from that outside the capsule, and (4) evidence of compression of adjacent thyroid tissue.

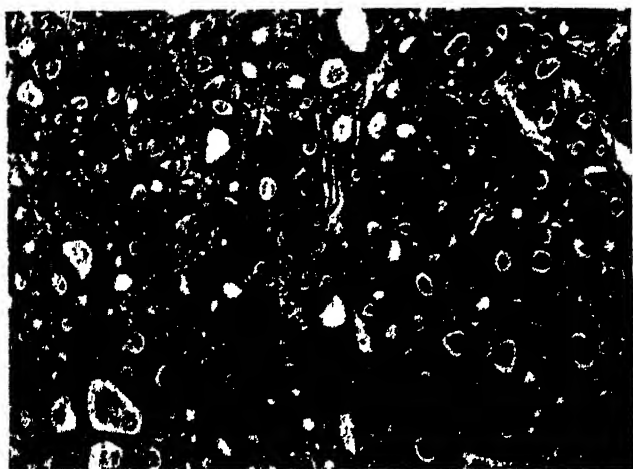


Fig. 246.—Thyroid, Hurthle cell tumor.

Papillary adenoma is a variety composed of papillary, or cystadenomatous, structures. **Colloid adenoma** is composed of differentiated thyroid follicles containing colloid. Their distinction from areas of colloid involution in a nodular goiter may be difficult. **Embryonal** and **fetal adenomas** are so called because of resemblances to embryonic or fetal thyroid tissue. The embryonal type is composed of cords and trabeculae of cells with little tendency to gland formation. The fetal adenoma consists of small follicles lined by low epithelium and often separated by abundant hyaline colloid-like material, or abundant and edematous stroma.

Hurthle Cell Tumor.—Hurthle cell tumors are composed of large, polyhedral cells, with prominent granular nuclei and abundant pale eosinophilic cytoplasm. The cells are arranged in solid-looking masses and clumps, but with formation of small alveoli. Stroma is usually small in amount. The origin of the distinctive cells is uncertain. Possible origins which have been considered are from (1) "parafollicular" cells, (2) nests of lateral thyroid anlage, and (3) parathyroid tissue. The microscopic resemblance to parathyroid adenoma may be very striking but the functional disturbances characteristic of parathyroid tumors are lacking. Benign and malignant forms occur. Criteria for malignancy are the same as in other thyroid tumors, vascular invasion being most important.

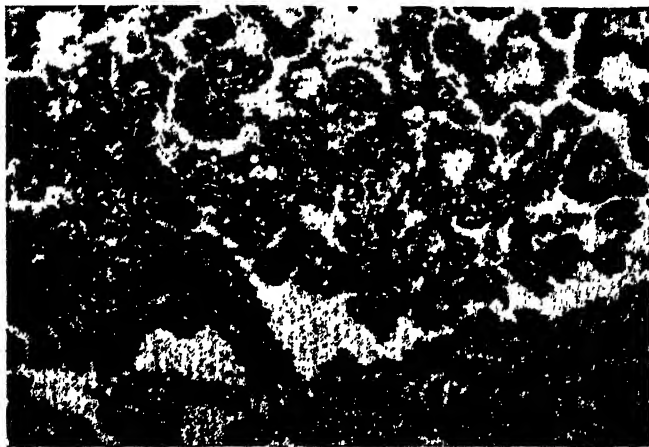


Fig. 247.—Papillary carcinoma of thyroid.

Carcinoma of the Thyroid.—Carcinoma of the thyroid arises most often from a benign adenoma and may be histologically well differentiated, so that diagnosis and prognosis are often very difficult. Invasion, and particularly vascular invasion, may be the only evidence of malignancy. Some of the well-differentiated tumors which invade blood vessels and produce secondary growths in other organs have been given the anomalous name of "benign metastasizing struma."⁸⁶ On the other hand, not all thyroid tumors in which vascular invasion is evident develop metastases or proceed in a clinically malignant fashion. Nevertheless, invasion is still the most reliable microscopic evidence of ma-

lignancy.³⁴ In many cases the usual histologic criteria of malignancy can be applied.

The common histologic types are papillary carcinoma and alveolar adenocarcinoma. They have a moderate degree of malignancy. Lateral aberrant thyroid tissue is particularly apt to give rise to papillary carcinoma.³⁷ However, many such thyroid tumors in the lateral cervical region have been shown to be metastases from an inconspicuous primary carcinoma in the normally situated thyroid gland. Small cell, spindle cell, giant cell, and other undifferentiated varieties occasionally occur and are of high malignancy.

Spread of thyroid cancer may be to adjacent tissues and lymph nodes, but blood stream metastasis to lungs and skeleton is common. Well-differentiated thyroid tissue in metastases will take up radioactive iodine, whereas undifferentiated thyroid tumor tissue does not store the tagged iodine.³⁸

Struma Ovarii.—Struma ovarii is a teratoma of the ovary in which thyroid tissue is the sole or chief constituent. Malignancy and metastasis may occur. Functional activity of the tissue is rarely sufficient to produce clinical hyperthyroidism.

THE PARATHYROID GLANDS

Structure and Function.—The parathyroids are usually four in number and situated on the posterior surface of the thyroid, or embedded in the thyroid tissue but separated from it by a connective tissue capsule. There is considerable variation in their position, particularly in the site of the lower pair, which are derived from the third branchial pouch in close association with portions of the thymus. One or both of the lower parathyroids may be found in the mediastinum in or near the thymus.

Histologically, the gland contains three main types of cells: (1) small dark "chief" cells; (2) clear "chief" cells (*wasserhelle* or water-clear cells); (3) oxyphilic cells. The clear chief cells are thought to be the precursors of the other types. They have a clear nongranular cytoplasm and a large pale nucleus. The oxyphilic cells are larger, have a granular acidophilic cytoplasm and a small dark nucleus. The small dark cells have a finely granular cytoplasm which stains faintly with eosin, and a small dark nucleus. Glycogen is found in considerable quantity in the parathyroid tissue, particularly in the chief cells. The cellular elements in the nor-

mal gland may be diffuse or compact, but usually have a definite arrangement in irregular strands or trabeculae. There may be occasional acinar arrangement. Fat cells are often quite abundant between the parenchymal cells. The parathyroids are important in the regulation of calcium and phosphorus metabolism. Parathyroid regulation maintains the diffusible ionized portion of serum calcium (i.e., the portion of serum calcium not bound to protein), within a narrow normal

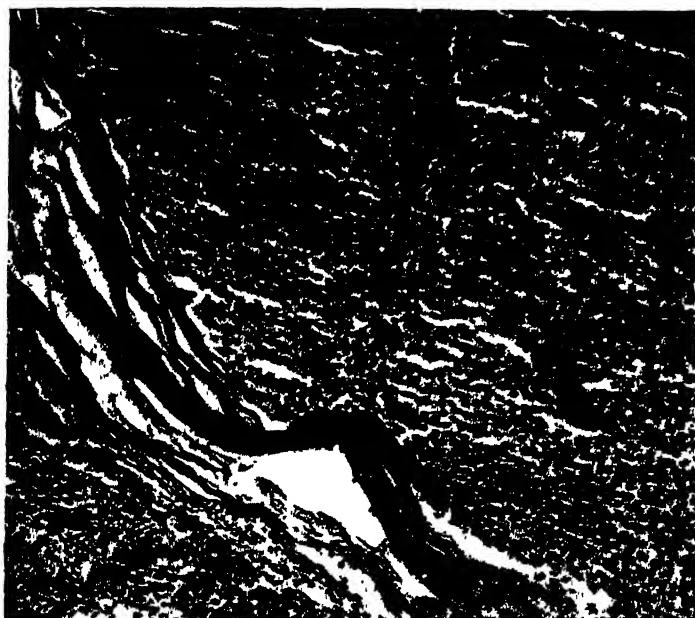


Fig. 248.—Adenoma of parathyroid, chief cell type.

quantitative range. The mechanism of regulation appears to be by promotion of renal phosphate excretion, and through mobilization of calcium from bones by stimulation of osteoclasts. It is thus evident that disturbances of parathyroid hormone production may be expected to produce changes in calcium and phosphate regulation, with lesions not only in the parathyroids themselves, but also in bones and kidneys. Hypoparathyroidism, or insufficient hormone production, is associated with tetany (neuromuscular irritability). Hyperparathyroidism, in which there is excessive hormone, may

result in the skeletal changes of osteitis fibrosa cystica, calcium deposits in soft tissue (metastatic calcification), and renal calculi.

Hyperparathyroidism.—Hyperparathyroidism may be primary or secondary. The primary form originates in the parathyroids either as a tumor (adenoma) of one gland or rarely as an idiopathic hypertrophy of all glands. In secondary hyperparathyroidism there is diffuse hyperplasia of all glands. A mild degree of such secondary parathyroid hyperplasia occurs in chronic renal disease, osteomalacia and rickets, and may be produced experimentally by phosphate injections. Long-standing chronic renal insufficiency may produce pronounced parathyroid hyperplasia and in turn skeletal changes (renal dwarfism, renal hyperparathyroidism—see p. 302).

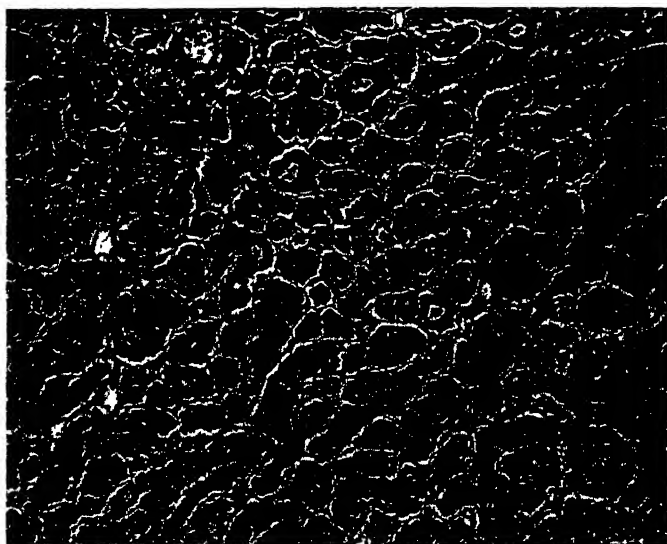


Fig. 249.—Parathyroid adenoma.

Parathyroid adenoma is a benign tumor involving a single gland or portion of a gland. It is most commonly composed of chief cells, less commonly of large “water-clear” cells or of oxyphiles. The cellular elements are compactly disposed, with loss of trabecular arrangement of cells and decrease of fat and connective tissue. Acini are often numerous, but

there is variability of cellular arrangement. Individual cells may be increased in size and contain multiple nuclei. Malignancy is rare, but functioning metastases have been reported.

Primary idiopathic hypertrophy of the parathyroids has been described by Albright and his colleagues.⁴⁰ All the glands are enlarged and of uniform structure, being composed of extremely large cells having a very clear cytoplasm. This type of hyperparathyroidism is very rare.

Secondary hyperparathyroidism is characterized by enlargement of all the glands due to increased numbers of nor-

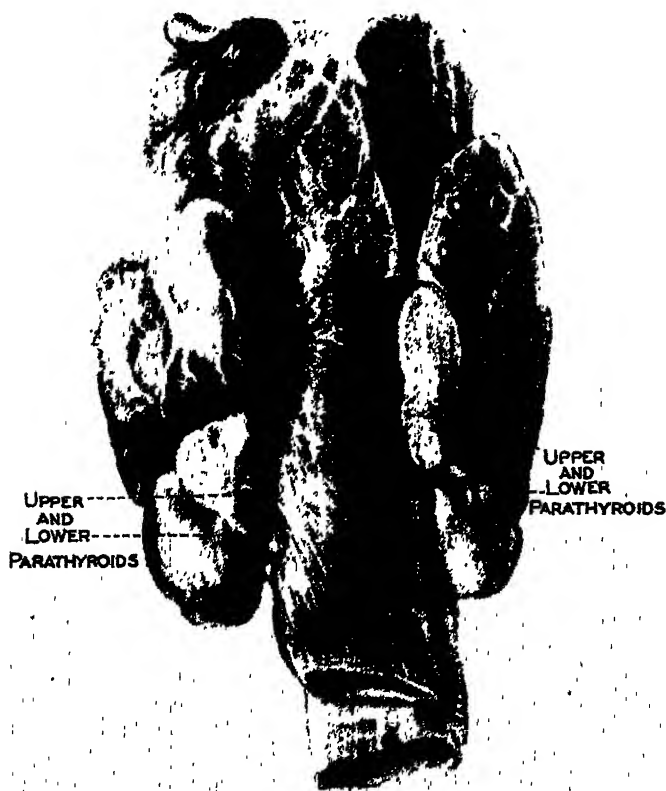


Fig. 250.—Parathyroid hyperplasia. Marked enlargement of all parathyroids in a case of renal dwarfism.

mal small dark "chief" cells. The various glands are not necessarily enlarged to the same degree, but all show decrease of interstitial fat.

Hyperparathyroidism is characterized clinically by weakness, polyuria, pain in the bones and skeletal changes, increased serum calcium and phosphatase, and decreased serum phosphate. The bony changes on x-ray may appear as a uniform osteoporosis, or the decalcification may be associated with cyst formation. Renal or skeletal disease is usually prominent. Renal disease in association with hyperparathyroidism is discussed on p. 302, and the hyperparathyroid skeletal disease, *osteitis fibrosa cystica*, on p. 649.

Hypoparathyroidism.—Manifested clinically by tetany, hypoparathyroidism is most commonly seen following operations upon the thyroid gland, in which parathyroids have been accidentally removed or their blood supply disturbed. Idiopathic cases also occur.

Tetany is a manifestation of neuromuscular hyperirritability due to low blood and tissue calcium and occurs also in conditions other than hypoparathyroidism, such as rickets, osteomalacia, and hyperventilation.

THE THYMUS

Structure and Function.—The thymus is an epithelial and lymphoid structure prominent during childhood. Its relative size is greatest at time of birth, when it weighs about thirteen grams, and its absolute size is greatest at puberty when the average weight is about thirty grams. In adult life it undergoes atrophy and replacement by fatty tissue.

The epithelial elements are derived from the third branchial cleft, and the lymphoid structures develop later in fetal life. The epithelial cells form concentric collections known as Hassall's corpuscles. The function of the thymus is unknown, and while exhibiting changes in certain endocrine disturbances, there is no direct evidence that the organ has any internal secretion. It is probably more correctly considered as a lymphoid structure. Rowntree and his associates have found that administration of thymic extracts to successive generations of rats results in precocity of growth and development. Shay and his collaborators⁴² have found that destruction of the thymus by radiation in young male rats arrests testicular development and produces pituitary changes typical of castration, but the changes are not permanent.

Like other lymphoid structures the thymus is highly sensitive to radiation. Pathologic changes in the thymus are rare and consist of atrophy, hyperplasia, and tumor formation.

Atrophy.—In addition to the physiologic atrophy which occurs after puberty, an atrophy occurs in most serious illnesses or infections of childhood.

Hyperplasia.—Hyperplasia of the thymus occurs in hyperthyroidism (Graves' disease), acromegaly, some cases of Addison's disease, and in eunuchs. In infants or young children an enlarged thymus may occasionally cause respiratory compression and produce symptoms of dyspnea, cyanosis, stridor, etc.⁴³

STATUS THYMO-LYMPHATICUS.—The concept of status thymo-lymphaticus is that of a constitutional abnormality in certain persons characterized by enlarged thymus, generalized lymphoid hyperplasia, hypoplasia of the aorta, atrophy of the adrenals, and underdevelopment of testes or ovaries. Such individuals are supposedly subject to sudden death as a result of relatively trivial stimuli, e.g., mild trauma, anesthesia, etc. It is probable that the thymus plays no role in the condition other than being part of the generalized lymphoid hyperplasia. That such a condition actually exists is often doubted.

Tumors.—Tumors of the thymus are rare. About one-half the cases of myasthenia gravis are associated with a benign tumor of the thymus (thymoma). **Myasthenia gravis** is a condition of weakness or abnormal fatigability of muscles. It is believed due to some interference with the transmission of impulses across the myoneural junction, a condition temporarily overcome by administration of prostigmine and simulated by curare poisoning. Lymphocytic infiltrations (lymphorrhages) are found in affected muscles. The nature of the association of the condition with the thymus is uncertain. The thymic tumors sometimes have been characterized by epithelial metaplasia.⁴⁵ In many, but not all cases of myasthenia gravis in which thymic tumor is absent, a thymic hyperplasia of lymphocytic cells has been found, without a generalized lymphoid hyperplasia. Surgical removal of the thymus has been reported to have improved some cases. Other conditions in which occur similar hypertrophy of the thymus, muscular weakness, and creatinuria are hyperthyroidism, adrenal cortical deficiency, and castration.^{46, 47, 48} **Malignant tumors** of the thymus may arise either from the epithelial structures (carcinoma) or from the lymphoid elements (lymphosarcoma).⁴⁵ **Dubois' abscess** is a cyst of the

thymus due to persistence of the embryonic duct which gives rise to the epithelial structures. It may be associated with congenital syphilis.

THE PINEAL BODY

Structure and Function.—The function of the pineal body is as yet unknown, though possibly it is concerned with changes occurring at puberty. There is some evidence that it has a secretory function, though it is not essential to life, pregnancy, or parturition.

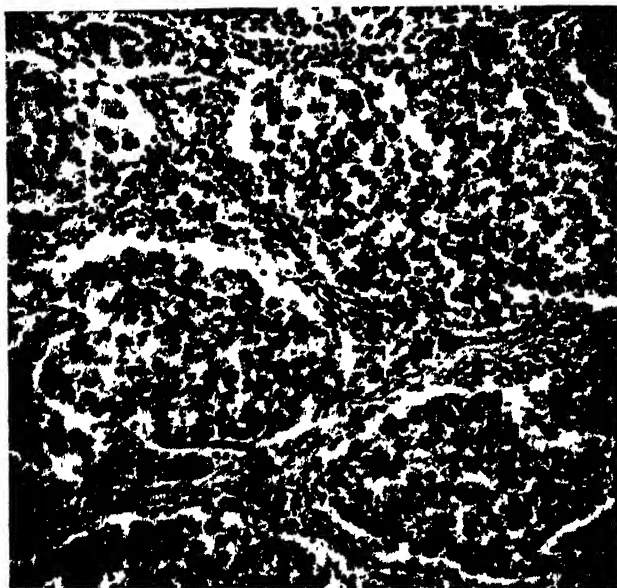


Fig. 251.—Pinealoma, showing the two types of cells usually present.

About the time of puberty regressive structural changes are initiated in the pineal. There are an increase in interstitial connective tissue and accentuation of fibrous trabeculae which give the gland a lobulated appearance in microscopic section. Calcareous concretions (acervuli) also begin to form about puberty and are practically constant after the sixteenth year. In adult life they are sometimes sufficiently dense to be evident on an x-ray plate.

Areas of neuroglial hyperplasia, often with irregularly cavitated centers, are quite commonly present in the pineal. True cysts also occur, usually lined by ependymal cells. Granules occur constantly in the cytoplasm of the pineal parenchymal cells during adult life and suggest a possible secretory activity.

Tumors.—Tumors of the pineal constitute its only important lesion. Pineal tumors are of three types, (1) pinealomas, (2) teratomas, and (3) gliomas.

Pinealomas are tumors composed of pineal parenchymal cells and have a microscopic appearance similar to that of some stage of embryonic development of the pineal.^{49, 50} Two types of cells are usually present: large pale cells with prominent rounded nuclei and indefinite cytoplasm, resembling cells of the adult period, and fewer small round, dark cells resembling lymphocytes. The tumor is locally invasive and malignant. Pinealomas also may have a structure resembling the adult pineal. While some evidence has suggested that the usual pinealoma is really an atypical teratoma,⁵¹ there are also teratomas of the pineal which are similar to teratomas elsewhere, containing bone, teeth, cartilage, epithelium, hair, etc. **Gliomas** of the pineal usually closely resemble the ependymomas which arise in other areas of the brain but spongioblastic pineal tumors also occur.

Because of their situation, pineal tumors soon obstruct the aqueduct of Sylvius, producing internal hydrocephalus and marked increase of intracranial pressure. Certain pineal tumors in preadolescent boys have been associated with precocious sexual development (pubertas praecox or macrogenitosomia praecox). A similar condition of hypergenitalism has been associated with midbrain lesions or tumors, as well as with various endocrine disturbances.

THE ADRENAL GLANDS

Structure and Function

The adrenals consist of two distinct glands, cortex and medulla, which have different origins and functions. The cortex is of mesodermal origin, from the urogenital ridge and is thus closely related to gonads and other urogenital organs. The medulla originates from the neural crest in common with sympathetic nerve cells. While anatomically associated in man, the cortex and medulla are quite separate in their function and pathology and are best considered as separate glands. The cortex, which is essential for life, is associated with salt

and water metabolism, and with development and maintenance of secondary sexual characteristics. The adrenal medulla secretes epinephrine (adrenalin) the effects of which simulate sympathetic stimulation. Survival is possible in the absence of the medulla.

The adrenals are relatively largest at time of birth, when they are usually one-third the size of the kidney. The large size is due to an extra layer in the inner part of the cortex. This highly vascular region disappears almost entirely during the first year of life. In adult life the adrenals are about one-thirtieth the size of the kidney.

ADRENAL CORTEX

The adrenal cortex is divided into zones descriptively named, from without inward, the glomerulosa, fasciculata, and reticularis. Internal to these the highly vascular zone which exists at time of birth is replaced by a thin "juxta-medullary zone." Some brownish pigment, of no known significance, is often present in the inner part of the cortex. The cortical cells normally contain abundant lipid in their cytoplasm, which gives them a somewhat foamy appearance. The functional relationships of the adrenal cortex to salt and water metabolism, ascorbic acid, pigmentation, blood pressure, and sexual characteristics are best illustrated by the effects of disease of the glands.

Lesions in the adrenal cortex may roughly be grouped as (1) regressive and destructive changes; (2) hyperplasia and tumors.

Regressive and Destructive Lesions.—

AUTOLYSIS.—Softening and central cavitation of the adrenals are a common autopsy finding, generally attributed to post-mortem degeneration. Its rapid occurrence appears to be related to a low ascorbic acid level in blood plasma (below 70 mg. per cent). The adrenal cortex normally stores vitamin C in large amounts.

HEMORRHAGE AND NECROSIS.—Extensive hemorrhage into adrenals or thrombosis of adrenal vessels may produce acute adrenal insufficiency. Hemorrhage is particularly common in newborn infants, in some cases from trauma incident to birth. Adrenal hemorrhage or focal necrosis may also occur with extensive burns or in various infections. Small areas of hemorrhagic necrosis may occur in eclampsia. In newborn infants the highly vascular inner zone of the cortex may be mistaken for hemorrhage unless carefully examined.

Various acute infections may severely damage the adrenal cortex, transforming the solid cords of cells of the zona fasciculata into tubular structures containing inflammatory exudate. Rich⁵⁵ has suggested that the adrenal damage may bear some relation to the circulatory collapse which occurs in some of these patients.

Massive bilateral hemorrhages of the adrenals are common in cases of fulminating meningococcemia, in which rapid death occurs, often before there is any marked involvement of the meninges (Waterhouse-Friderichsen syndrome).⁵⁸ The fatal outcome appears to be due to the overwhelming meningococcemia, acute adrenal insufficiency having but a minor role.⁵⁹ The hemorrhages in the adrenals, skin, and elsewhere appear to be the result of toxic injury of capillary endothelium.

ADDISON'S DISEASE.—Chronic adrenal cortical insufficiency produces the clinical condition of Addison's disease. Symptoms appear when about 80 per cent of adrenal cortical tissue has been destroyed. In about 70 per cent of cases the bilateral destruction of adrenals is due to tuberculosis. In most of the remaining cases there is atrophy or destruction from unknown causes, by some thought due to unsuspected chemical or drug poisoning. In the United States, cortical necrosis or atrophy appears to account for about 50 per cent of cases. In the case of the tuberculous lesions both cortex and medulla of the glands are usually destroyed. With cortical necrosis or simple atrophy the medulla may be unaffected. The medulla evidently is unimportant, except for the pigmentary changes, in the pathogenesis of Addison's disease. Inflammatory changes, fibrosis, and amyloid degeneration of the cortex are sometimes causative of Addison's disease, but bilateral metastatic tumors or gummas only rarely. In the tuberculous type of adrenal destruction, active tuberculous lesions usually are found elsewhere.

Addison's disease is characterized by extreme weakness, low blood pressure, and pigmentation of the skin. The pigmentation is due to excessive melanin, resulting from disturbed melanogen metabolism, in which the adrenals and the production of epinephrine seem to be concerned. It may be irregular in distribution, and often is best seen in the mucous membranes of lips or mouth, or in scars. Urinary excretion of ketosteroids is decreased to a low level. Salt metabolism is disturbed, there being excessive loss of sodium salt in the urine. High sodium and low potassium intake relieves many



Fig. 252.—Tuberculosis of adrenal glands (Addison's disease). (Courtesy Dr. H. O. Schmeisser.)

of the symptoms. Adrenal cortical extracts, particularly "desoxycorticosterone," also assist in overcoming the hormonal deficiency.

LIPOID DEPLETION.—Shock, acute intestinal obstruction, various inflammatory diseases, and cachexia may be reflected in the adrenal cortex by lipoid depletion or change in the pattern of distribution of lipoid in the adrenal cortex.⁵⁴

ANENCEPHALY.—The adrenals have frequently been reported as defective or absent in anencephalic monsters. According to Angevine⁵⁵ the adrenals are present but atrophic, and histologically of adult rather than infantile type. The adrenal atrophy is believed secondary to pituitary changes.

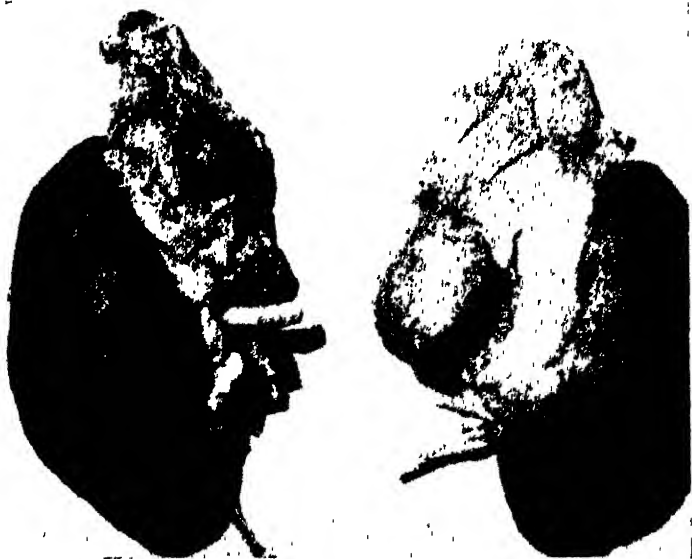


Fig. 253.—Bilateral adenomas of the adrenals. The situation in relation to the kidneys is shown. (Courtesy Dr. H. C. Schmeisser.)

Hyperplasia and Tumors.—Hyperplasia in the adrenal cortex may be diffuse but often takes the form of small circumscribed nodules which vary from microscopic size to a diameter of several centimeters. The small nodules occur as an incidental finding in a considerable proportion of autopsies on adults. They probably represent a regenerative process following infection or other injury of the adrenals. Microscopically, they consist of columns of adrenal cells like those

of the fascicular zone. True adenomas also occur as yellowish masses which may grow to considerable size. Although well circumscribed, they may press upon and deform the remainder of the gland. Carcinomas are similar to the adenomas but contain areas of atypical and malignant-looking cells, and they metastasize readily.

In a certain proportion of cases the hyperplasias, adenomas, and carcinomas are associated with abnormal sexual characteristics. These have been considered to be distinguishable by the Ponceau-fuchsin stain, devised by Vines, which shows the presence of red fuchsinophile granules in the cells, although the specificity of this reaction has been questioned. An androgenic (male) hormone has been extracted from such tissue.⁵⁷



Fig. 254.—Adrenal adenoma (microscopic appearance of tumors shown in Fig. 253). (Courtesy Dr. H. C. Schmeisser.)

Overgrowth of the cortical tissue which produces the male hormone causes a variety of sexual disturbances depending upon the age at which it occurs. The androgenic tissue is normally present in the adrenal during certain periods of fetal life. Abnormal growth or persistence in a female fetus produces pseudohermaphroditism. Occurring in boys, sexual precocity develops, with genitalia of adult size and secondary sexual characteristics. (Sexual precocity

in boys may also result from pineal, testicular, and cerebral tumors.) In girls, pseudosexual precocity with maleness occurs, with the appearance of pubic hair and hypertrophy of the clitoris to resemble a small penis. Adult females become masculinized (virilism or the adrenogenital syndrome), the change being characterized by hirsutism, enlarged clitoris, atrophy of breasts, amenorrhea, and various masculine characteristics. The Achard-Thiers syndrome (diabetes of a bearded woman) appears to be a variant in which adrenal virilism has the added feature of diabetes mellitus. Some cases of adrenal cortical hyperplasia or tumors in adult females have obesity, hypertension, and disturbances in carbohydrate metabolism and may be indistinguishable from Cushing's syndrome (see p. 518). Virilism due to an arrhenoblastoma of the ovary also may closely simulate the adrenogenital syndrome.

In cases having an adrenal cortical adenoma or carcinoma the opposite adrenal may be atrophic, and insufficient to meet sudden functional demands. Consequently, an acute adrenal insufficiency may develop following surgical removal of the tumor.

Various adrenal changes have been described as associated with hypertension. Increase in weight of the adrenals, with nodular hyperplasia of the cortex and a high lipid content has been described in essential hypertension,^{54, 62} although others have denied that there is any constant association.⁶³ Hyperplasia of the medulla has been noted in renal disease and hypertension,⁶⁶ and hypertrophy of the musculature of adrenal veins has been emphasized.⁵²

THE ADRENAL MEDULLA

The medulla of the adrenal has an origin from ectoderm in common with sympathetic nerve tissue. The cells of the medulla stain with chrome salts as do certain other tissues, such as abdominal paraganglia and the carotid body. Their function of epinephrine production is not essential for life. Functional disturbances caused by destructive lesions of the medulla are overshadowed by the associated involvement of the cortex, as in the tuberculous type of Addison's disease. The only lesions of the adrenal medulla of practical importance are tumors.

Tumors.—Tumors of the adrenal medulla or other parts of the sympathetic nerve system are composed of immature or mature cell types comparable to those which occur in embryonic development of medullary and sympathetic nerve

tissue. The most immature form, the precursor of the other types, is the sympathogonia, a small dark lymphocyte-like cell, which differentiates into neuroblasts (sympathoblasts and pheochromoblasts). The sympathoblasts mature as ganglion cells, and the pheochromoblasts develop into pheochromocytes, the mature cells of the adrenal medulla. Tumors composed of the immature forms (sympathogonioma and neuroblastoma) are highly malignant, while those composed of mature forms (ganglioneuroma and pheochromocytoma) are benign.

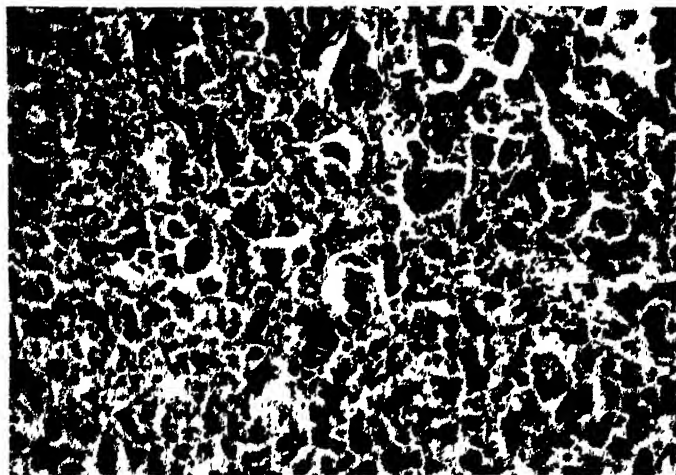


Fig. 255.—Carcinoma of the adrenal cortex. The tumor cells show marked variation in size, shape, and intensity of staining.

Sympathogoniomas usually develop during intrauterine life or in early infancy, are highly malignant and invasive, and metastasize early. They are composed of small dark cells resembling lymphocytes, some of which group to form rosettes. No neurofibrils are formed.

Adrenal neuroblastoma (sympathoblastoma) is a highly malignant tumor which occurs almost exclusively in infants and young children. It arises either in the adrenal medulla or the immediate neighborhood. Microscopically, it is extremely cellular, composed of small rounded dark cells resembling lymphocytes, and it has the characteristic feature of a circular grouping or pseudorosette formation around a fine fibrillar network. It differs from the sympathogonioma only in its somewhat greater maturity, and some differenti-

ated ganglion or pheochromocytoma cells may be present. The cells tend to be larger, irregular or oval in shape, and may have elongated cytoplasmic processes. Tumors having similar histologic structure are the medulloblastoma of the midbrain and the retinoblastoma of the eye. They also arise from undifferentiated neural elements and occur in childhood.



Fig. 256.—Neuroblastoma of the adrenal medulla. The kidney can be seen below the tumor. (Courtesy Dr. H. C. Schmeisser.)

Adrenal neuroblastoma spreads early and widely and the clinical picture largely depends on the metastases. Tumors of the right adrenal tend to metastasize to retroperitoneal lymph nodes and liver, producing the "Pepper syndrome." Metastasis to bones, particularly of the skull and around the region of the orbits, produces the "Hutchinson syndrome," prone to result from a tumor of the left adrenal medulla. The two classical types frequently overlap.

GANGLIONEUROMA.—Ganglioneuroma is a benign tumor composed of differentiated, large, sympathetic ganglion cells and often a few nerve fibers. It may occur in either child or adult. While the common origin is from adrenal medulla.

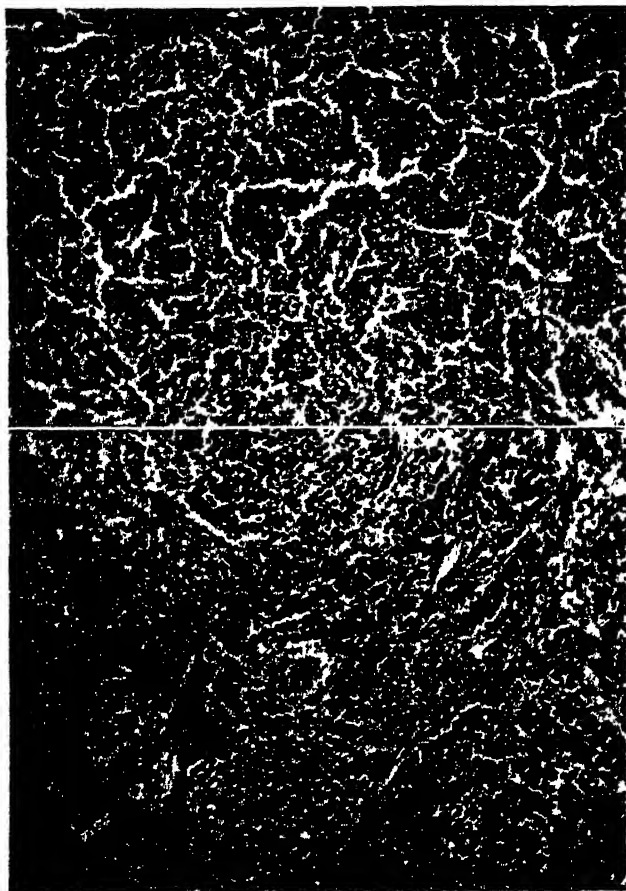


Fig. 257.—Neuroblastoma, adrenal medulla. Note the small, dark neuroblastic cells.

it may arise in any part of the abdominal sympathetic system or very rarely is found in the central nervous system. It produces symptoms only by virtue of the large size to which it may grow.

PHEOCHROMOCYTOMA.—Chromaffinoma (paraganglioma, pheochromocytoma) is a rare benign tumor composed of a differentiated mature type of cell resembling those which normally compose the adrenal medulla. The pleomorphic cells stain brown with chrome salts. The chromaffinoma usually occurs in middle age or beyond. Its chief interest lies in its association with paroxysmal hypertension, apparently due to a high adrenalin content of the tumor tissue.

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CHAPTER XXI

FEMALE GENITAL ORGANS

The important pathologic conditions of the female genitalia are inflammations, endocrine disturbances, tumors, and cysts. Many gynecologic diseases are closely related in both functional and morphologic aspects to hormonal imbalance. The endocrine factors important in gynecologic pathology are the pituitary gonadotropic principles and the ovarian and placental hormones.

HORMONAL RELATIONSHIPS

Pituitary Gonadotropic Hormones.—There are two pituitary principles which act on the ovaries: (1) a follicle-stimulating hormone, which controls maturation of the ovarian follicles, and hence in turn the production of follicular hormone (estrogen); and (2) a luteinizing hormone which controls luteinization of the ruptured follicle, and hence in turn the production of the luteal hormone (progesterone). The nature and chemical structure of these pituitary principles are still unknown.

Ovarian Hormones.—The two ovarian hormones which normally are controlled in this fashion by the pituitary are of known chemical nature and structure, and they exert pronounced effects on the endometrium, vagina, and other tissues. Menstrual changes and periodicity are dependent on these hormones.

Maturing ovarian follicles produce a hormone, estrogen (theelin). This has been isolated in a number of closely related forms, all characterized by the ability to produce estrus (heat) in castrated animals. Various names given to these estrogens are estradiol, estrone, and estriol. Certain estrogenic substances can be derived synthetically (e.g., stilbestrol). The basic chemical structure of estrogens is the phenanthrene ring system. Thus there is a chemical structural resemblance to certain naturally occurring sterols and to some potent carcinogenic materials, a relationship which has caused much interesting speculation.

Estrogen, formed by the mature ovarian follicle, is a sexual growth-stimulating substance which acts especially on the uterus and vagina. It brings about the proliferative endometrial growth characteristic of the first half of the

menstrual cycle (see p. 583). In addition it controls the rhythmic activity of the uterine musculature, causes cornification of the vaginal epithelium, and growth of the duct system of the breast. At puberty, estrogen is responsible for the appearance of the various secondary sexual characteristics.

The ovarian follicle ruptures about the middle of the menstrual cycle and then forms the corpus luteum. This luteinized follicle produces not only estrogen, but also a new and characteristic hormone, progesterone. This latter substance also is a sterol, of known chemical formula, and has been isolated, crystallized, and synthesized. It has a close structural relationship to the male sex hormone, testosterone.

Progesterone also affects the endometrium, vagina, and breast. In the endometrium it brings about a secretory phase (see p. 584). The endometrium remains hypertrophied, but the glands become very irregular in outline and secretory in function. The stromal cells of the endometrium begin a decidua-like change. These changes are in preparation to receive the fertilized ovum. If conception fails to occur, the corpus luteum atrophies, the endometrium breaks down, and menstruation occurs. However, if pregnancy occurs, the corpus luteum continues to develop and produce progesterone, its effects being important in maintenance of the pregnancy in its early phases.

In addition to its effect on the endometrium, progesterone inhibits contractility of the uterus, suppresses ovulation and menstruation, causes a mucus-secreting phase in vaginal epithelium, and a lobular proliferation of the breast.

Hormones of Pregnancy.—During pregnancy chorionic gonadotropic hormones are produced and are found in the urine (urinary prolan). The biologic pregnancy tests (Aschheim-Zondek, Friedman) are based on demonstration of such hormones in the urine. These substances are "anterior-pituitary-like" (A.P.L.) in their action. The placenta also seems capable of producing progesterone, an action important in maintenance of later stages of pregnancy.

THE OVARIES

Development and Structure

The ovaries develop from the Wolffian body, along with other portions of the reproductive and urinary system. The ovary and testis have a similar anlage. In the early undifferentiated ovary medullary cords form, similar to those

of the early testis which later form the seminiferous tubules. Persistent remnants of these transient male-directed cells may later give rise to masculinizing tumors (e.g., arrhenoblastoma). Enormous numbers of primitive follicles develop as the ovary differentiates. The cortex of the ovary is composed of these primitive Graafian follicles and a dense connective tissue stroma. The so-called epithelial cells of the follicles (i.e., granulosa cells) and the stromal cells (including theca cells, which are specialized stromal cells around follicles) have a common mesenchymal origin. Their close relationship is evident in certain tumors (e.g., theca-cell tumors). The primordial follicles consist of a central ovum surrounded by a layer of low cuboidal epithelium, the granulosa membrane. As the follicle matures and enlarges under the influence of the pituitary follicle-stimulating hormone, the granulosa becomes more cuboidal and several layers thick. A central cavity appears, the ovum being at one pole, surrounded by a pile of granulosa cells, the discus proligerus. Around the follicle is a specialized layer of connective tissue cells, the theca interna. Call-Exner bodies are small, rounded, clear, gland-like areas found in the granulosa layer, and similar structures appear in tumors composed of granulosa cells. About the middle of the menstrual cycle the follicle ruptures, and the ovum is extruded. The ruptured follicle develops into a corpus luteum under the influence of the luteinizing hormone of the pituitary.

At the time when the follicle ruptures, many other follicles are approaching maturity. Their further development is stopped by the hormone of the corpus luteum, and they undergo regression. These atretic follicles form cysts, and in some cases the cysts reach a considerable size. Usually the cystic stage is promptly followed by fibrosis, forming a small hyalinized area, the corpus fibrosum.

In development of the corpus luteum following follicular rupture, the granulosa is vascularized, and the cells become large and polyhedral, with abundant vacuolated cytoplasm. They are then called lutein cells and form a bright yellow zone. Hemorrhage into the follicular lumen usually occurs, and in some cases this is abundant. The mature corpus luteum is much larger than the follicle, measuring up to 10 or 15 mm. in diameter.

If fertilization does not occur, regression of the corpus luteum begins shortly before menstruation. Fatty change of the lutein cells is followed by atrophy, fibrosis, and hyalinization. This results in a convoluted hyalinized mass, the

corpus albicans, which slowly regresses further and disappears. Occasionally the corpus luteum fails to regress but develops into a cyst (corpus luteum cyst). Also, if pregnancy occurs, the corpus luteum does not regress but becomes even larger and more prominent.

Inflammation (Oophoritis)

Inflammation of the ovary is secondary to inflammation elsewhere, most commonly spreading from the tube. Oophoritis secondary to tubal infection is usually due to the gonococcus, streptococcus, or tubercle bacillus. Occasionally there is hematogenous infection of the ovary, as in mumps. Inflammatory reactions in the ovary are similar to those elsewhere. Acute and chronic abscesses are common. An abscess often involves a corpus luteum, the organisms apparently gaining entrance to the ovary through a ruptured follicle. Oophoritis is followed by fibrosis and adhesions to surrounding structures.

Tuberculous oophoritis is practically always secondary to tubal tuberculosis. Tuberculous peritonitis is usually present as well. The microscopic picture is the same as in tuberculosis elsewhere.

Cysts of the Ovary

Cysts of the ovary are of two main groups: (1) retention cysts, i.e., dilated glandular structures, and (2) neoplastic cysts, i.e., cystic tumors. The latter will be considered with other ovarian tumors.

Ovarian retention cysts sometimes rupture and cause intraperitoneal hemorrhage.² The clinical aspects depend on the amount of intraperitoneal hemorrhage, which in rare cases may be quite massive. Clinical differentiation of such cases from other acute abdominal conditions may be difficult. Non-neoplastic cysts are of four main types.

1. **Follicular cysts** are due to distention of an unruptured Graafian follicle. They are extremely common and usually remain small in size, but occasionally they reach several centimeters in diameter. Lining granulosa cells are evident in the smaller cysts, but the larger cysts may be lined by a single layer of low cuboidal epithelium. Hemorrhage into the cyst occasionally occurs.

2. **Luteal cysts** result from dilatation of a corpus luteum. They are less frequent than the follicular type and must be distinguished from the normal corpus luteum hematoma, the

large corpus luteum of pregnancy, and the hemorrhagic cysts of endometriosis. Luteal cysts are recognized microscopically by remnants of granulosa-lutein cells found in the wall.

3. **Theca-lutein cysts** are found in the ovaries in association with chorionepithelioma and hydatidiform mole (see p. 595). These cysts are multiple, bilateral, and lined by theca-lutein cells; i.e., the lutein cells lining the cyst are believed to arise from the theca interna rather than the granulosa.

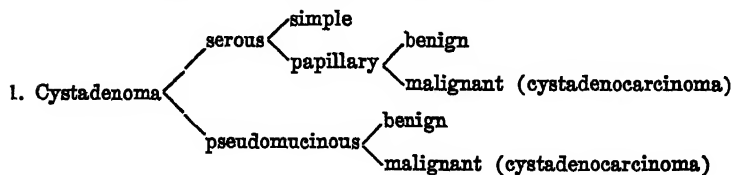
4. **Endometrial cysts**, or chocolate cysts of the ovary, are due to endometrial implants. They may reach a size of several centimeters, are often bilateral or associated with endometriosis elsewhere (see p. 589). Hemorrhage into the cyst cavity results in a thick chocolate-like content. This is not a distinctive feature, however, as a similar content may be found in hemorrhagic luteal cysts. Identification is by finding endometrial glands in some part of the cyst wall. Beneath the lining there is often a layer of swollen mononuclear phagocytic cells, containing blood pigment, and easily confused with luteal cells.

Tumors of the Ovary

Classification of ovarian tumors recently has been modified by the recognition of the endocrine function of various tumors. Herein they will simply be grouped into cystic and solid varieties, each group having both benign and malignant components. Those tumors with endocrine function are found among the solid tumors. A number of very rare types of ovarian tumors, e.g., ganglioneuroma, have been described but will not be considered here.

CYSTIC OVARIAN TUMORS

These tumors may be further classified as



2. Dermoid cysts.

Cystadenoma.—Cystadenoma is the commonest variety of ovarian tumor, the pseudomucinous type being of slightly greater frequency than the serous.

Serous cystadenomas may be unilocular or multilocular and sometimes reach enormous size. There may be a smooth lining of epithelial cells, but frequently there are papillary projections into the cavities. This papillary growth may be so marked that the tumor appears almost solid. The lining cells of the cyst are cuboidal or columnar epithelium, and



Fig. 258.—Ovarian cysts, showing characteristic linings. *A*, Dermoid cyst, with keratinizing squamous epithelium and sebaceous glands; *B*, serous cystadenoma, lined by dark-staining cuboidal cells; *C*, pseudomucinous cystadenoma, lined by pale columnar cells with basal nuclei; *D*, corpus luteum cyst, lined by a thick layer of large luteal cells. (From Berman, J. K.: Synopsis of the Principles of Surgery.)

sometimes ciliated. Calcium deposits are common in the papillary masses.

The simple cysts are benign, but the types with papillary overgrowth are frequently malignant. Invasive growth through the cyst wall results in papillary masses on the outer surface of the cyst. These may break off and implant throughout the peritoneal cavity. The cyst cavity contains a clear fluid with a rich content of serum proteins. The origin of the cysts is believed to be from germinal epithelium.



Fig. 259.—Papillary cystadenocarcinoma of ovary. Note the papillary masses growing on the external surface of the cyst. (Courtesy Dr. H. C. Schmeisser.)

Pseudomucinous cystadenomas contain a mucoid or pseudomucinous material. They are thin walled, multilocular, and have a smooth lining without papillary growth. The cysts are lined by a single layer of tall columnar epithelial cells with basal nuclei and a clear secretory cytoplasm. Pseudomucinous cystadenomas do not become malignant as com-

monly as do the serous cystadenomas, but occasionally a proliferative adenocarcinomatous change occurs.

Rupture of a pseudomucinous cystadenoma implants the secretory epithelium over the peritoneal cavity. Continued secretory function of the implants causes accumulation of large quantities of gelatinous material in the abdomen, the condition called *pseudomyxoma peritonei*.

The exact origin of pseudomucinous tumors is debatable, but they are generally believed to be teratomatous, i.e., overgrowth of one type of teratomatous tissue to the exclusion of the remainder.



Fig. 260.—Dermoid cyst of ovary. Note the hair and sebaceous material filling the cyst. (Courtesy Dr. H. C. Schmeisser.)

Parvilocular cystomas are tumors which grossly appear solid, but microscopically are found to have many cystic cavities, glandular structures or tubules lined by mucin-producing epithelium and embedded in fibrous stroma. They may become malignant. An origin from fetal remnants of the rete ovarii has been suggested.⁸

Dermoid Cyst.—Cystic teratomas constitute about 10 per cent of ovarian cystic tumors. They are rounded masses, of any size up to that of a grapefruit, with an opaque, grayish wall. The cyst content is a greasy, grayish-yellow sebaceous material mixed with a variable amount of hair. The cyst lining tends to be rough or granular, and at one point is a small, raised or thickened area from which the hair arises.

Section through this dermoid tubercle shows skin tissue and appendages, which give rise to the cyst contents. In addition to squamous epithelium, sebaceous glands, and hair follicles, a variety of other tissues may be found, such as cartilage, bone, teeth, thyroid, glands, intestinal tissue, etc.

Dermoids of the ovary are benign tumors, but occasionally one element may become malignant. This is most frequently the squamous epithelium. The most popular theory of their origin is that they represent spontaneous growth of an ovum, i.e., an attempt of a germ cell to form a new individual under unfavorable circumstances.



Fig. 261.—Dermoid cyst of ovary. Hair, bone, teeth, and a pigmented tissue are evident. (Courtesy Dr. H. C. Schmeisser.)

• **Teratoma** of the ovary is the counterpart among the solid tumors of the dermoid cyst. It is rare, and unlike the dermoid cyst, is usually malignant.

Mesonephroma.—Schiller^s has described a distinctive type of cystic ovarian tumor in which the lining cells have an endothelial appearance, and which contains small structures resembling embryonic renal glomeruli. This glomerulus-like unit consists of a tiny cystic cavity lined by flat endothelium-like cells into which there is a projection containing a capil-

lary loop covered by a layer of columnar epithelial cells. Solid areas of stellate cells of endothelial appearance also are found. Schiller suggested that the tumor developed from misplaced fetal remnants of the mesonephros, and tumors of similar structure have been found in the kidney. The tumor may be found at any age, is not associated with endocrine effects, and usually is malignant. The response to radiation is variable but sometimes very good.

SOLID OVARIAN TUMORS

While less common than cystic neoplasms, the solid tumors of the ovary are of wide variety, some forms being quite rare. They may be classified into 3 groups: (1) benign solid tumors, (2) tumors with endocrine function, and (3) malignant tumors. Among the endocrine tumors, some are biologically benign, while others have a low grade of malignancy.

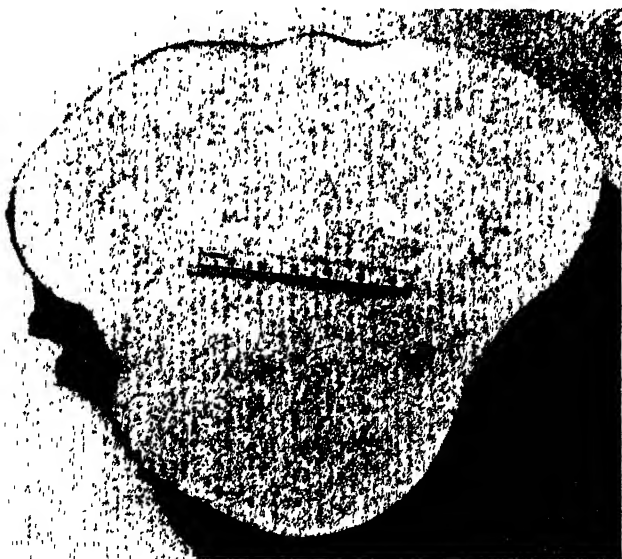


Fig. 262.—Fibroma of ovary. (Courtesy Dr. H. C. Schmeisser.)

Benign Solid Ovarian Tumors.—The only two common varieties in this class are fibromas and Brenner tumors.

Fibroma of the ovary is a firm, whitish, circumscribed tumor which may reach a considerable size. The cut surface is firm and may be homogeneous or trabeculated. Micro-

scopically, it is composed of well-differentiated, regular connective tissue, of uniform pattern and showing little evidence of active growth.

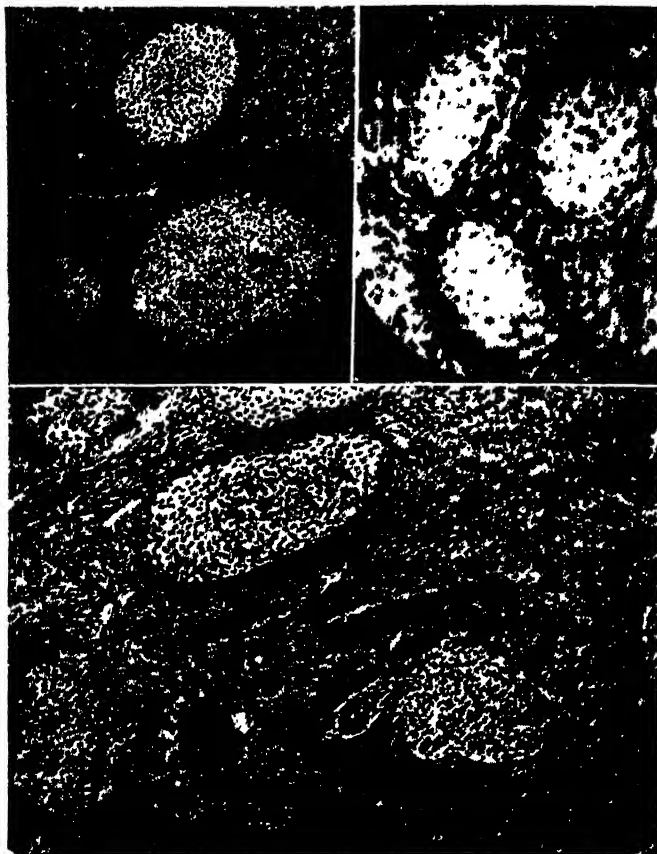


Fig. 263.—Brenner tumor of ovary. Small islands of tumor cells in a fibrous stroma.

Ascites is sometimes associated with ovarian fibroma, and as pointed out by Meigs,⁵ hydrothorax may be present as well, and disappear following removal of the tumor. The phenomenon is unexplained.

Fibromas must be distinguished from theca-cell tumors which have an endocrine function. While similar in many

respects to fibromas, theca-cell tumors have a more yellowish color in the gross, and microscopically they exhibit a high fat content.



Fig. 264.—Carcinoma of ovary.

Brenner tumors are uncommon benign tumors, usually found after the age of 50. They are without hormonal function. They are small firm circumscribed tumors, which occur alone or in the wall of a pseudomucinous cystadenoma. Grossly, they resemble a fibroma. Microscopically, they are characterized by islands or strands of epithelial cells, set in

a dense fibrous stroma. Frequently the nuclei of the epithelial cells have a characteristic longitudinal grooving or folding. Similar infolding may be evident in the nuclei of Walthard cell islands, giving them an appearance reminiscent of "Puffed Wheat."¹² Some of the epithelial islands may



Fig. 265.—Dysgerminoma of ovary. (Courtesy Dr. H. C. Schmeisser.)

have cystic centers, sometimes lined by columnar mucus-producing cells. Their origin is debatable, but may be (1) from tiny masses of undifferentiated cells occasionally found in the ovary, called "Walthard islands," (2) from a teratoma, as suggested by frequent association with pseudomucinous cystadenoma, (3) from displaced urogenital epithe-

lium, similar to that of the renal pelvis or ureter, or (4) from germinal epithelium of the ovary.

Malignant Solid Ovarian Tumors.—A number of solid tumors, of varying degree of malignancy but without endocrine effects, arise in the ovary. Only the more important types, carcinoma, sarcoma, and disgerminoma, are considered here. The Krukenberg tumor is a bilateral solid tumor, usually metastatic from the gastrointestinal tract.

CARCINOMA.—Primary solid carcinoma of the ovary is less common than the cystic type and is often bilateral. Probably many are cystic tumors in early stages. They are grayish brown, variable in size, shape, and consistency, and often have areas of necrosis. Microscopically, malignant epithelial cells may form well-defined glands (adenocarcinoma) or solid sheets of cells (medullary form). Extension is commonly to the other ovary, the peritoneum, and by lymphatics to lumbar and other lymph nodes. Occasionally blood stream spread involves distant organs.

SARCOMA.—Sarcoma of the ovary is much rarer than carcinoma. It may develop from malignant change in a fibroma or from the ovarian stroma. Grossly it is of moderate size, lobulated, and has a tendency to necrosis. Microscopically, it is usually a spindle-cell sarcoma.

DISGERMINOMA.—Disgerminoma (seminoma) is believed to arise from rests of undifferentiated (neuter) cells left over in development of the gonads. An entirely similar tumor (seminoma) occurs in the testicle. It has no hormonal effects, but it is often associated with congenital hypoplasia of internal genitalia or with pseudohermaphroditism. Such associated changes are not due to the tumor and remain after its removal.

Most disgerminomas occur before the age of 35, and sometimes are found during childhood. The degree of malignancy is variable. They form fairly large encapsulated or nodular tumors, of rubbery consistency, grayish-pink color, and friable cut surface. They are often bilateral.

Microscopically they are composed of cords and nests of cells with round hyperchromatic nuclei, and a small amount of indistinct pale cytoplasm. The cell cords are separated by loose fibrous trabeculae infiltrated with lymphocytes. Giant cells may be present. Mitoses are often numerous.

KRUKENBERG TUMORS.—Metastatic carcinoma of the ovaries due to spread from gastrointestinal tract or pelvic organs is quite common. Krukenberg tumors are a particular type of metastatic ovarian cancer, usually bilateral, in which the

tumor cells are mucus-producing. The distended cytoplasm and flattened nuclei of individual cells produce a signet ring appearance. The primary tumor is usually in the stomach (80 per cent), intestinal tract, or gall bladder and often is inconspicuous. The possible modes of spread to the ovaries are by retrograde metastasis along lymphatics and by peritoneal implantation. In rare instances a strikingly similar or identical Krukenberg type of tumor is primary in the ovary

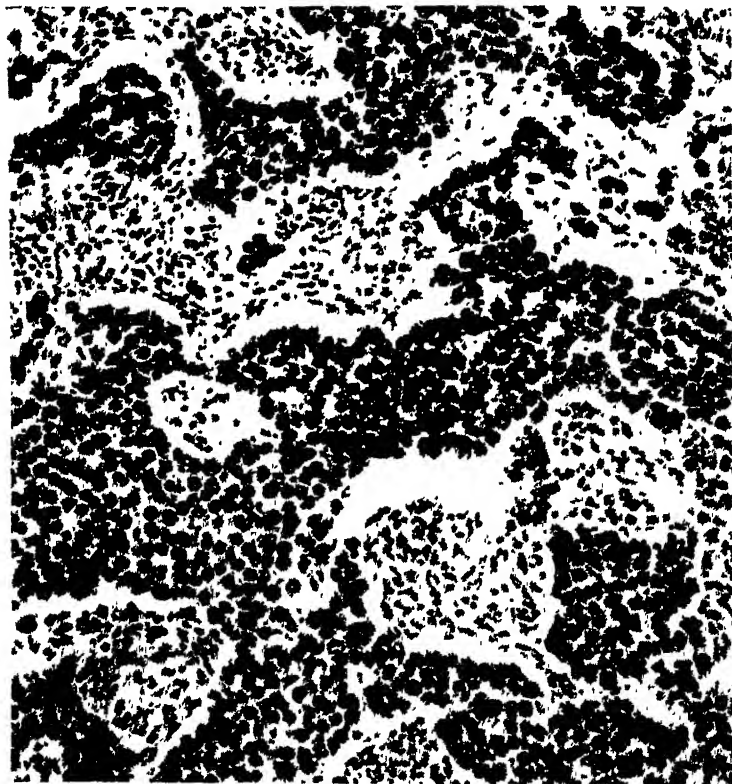


Fig. 266.—Disgerminoma of ovary. Note the rounded hyperchromatic nuclei, the scanty and indistinct cytoplasm, and the lymphocytes infiltrating the stroma.

Grossly the tumors are firm, solid, lobulated growths of moderate size, and have a variegated appearance on the cut surface. Microscopically, there are mucoid epithelial cells, of

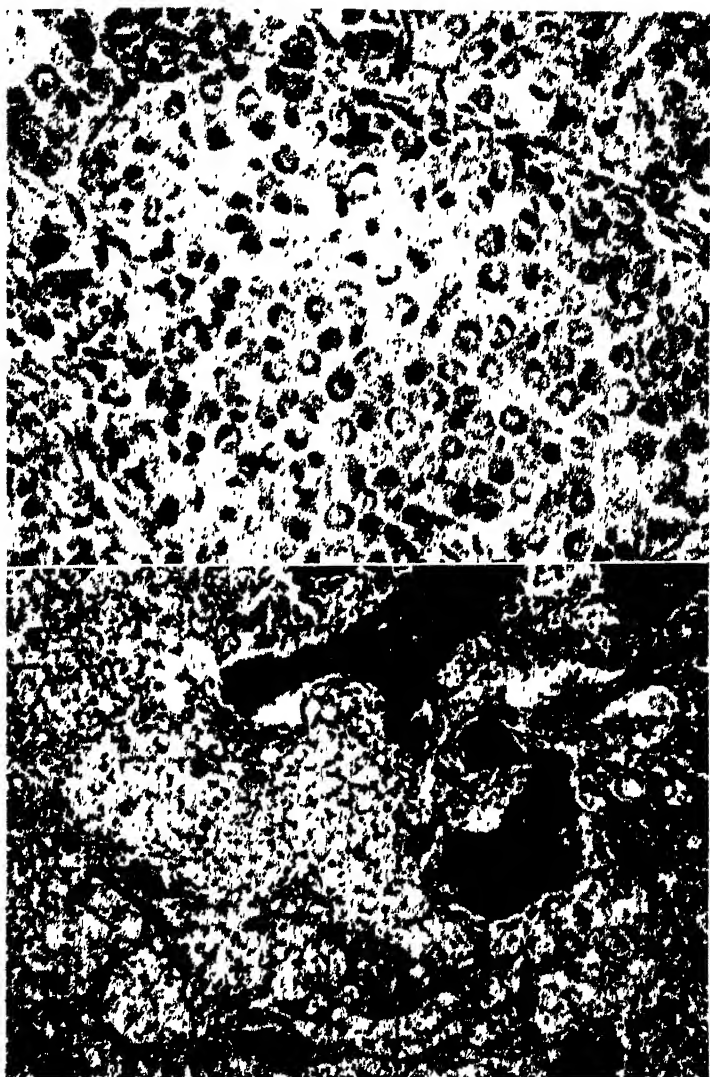


Fig. 267.—Krukenberg tumor. The lower figure shows a metastasis to bone. Note the "signet ring" cells.

signet ring appearance, arranged in solid masses or small clusters. Occasionally there is a tendency to gland formation. The stroma may be abundant and cellular. Since the tumor is usually the result of metastatic spread, the prognosis is often hopeless.¹³

ENDOCRINE TUMORS OF THE OVARY

Like other glands which produce hormones, the ovary gives rise to tumors whose cells have endocrine function as well as excessive growth energy, and in this fashion exert far-reaching effects upon the body. The endocrine function of the ovary is production of female sex hormones. The commonest endocrine tumors of the ovary are those which produce excess female sex hormones (estrogen). There are two such tumors, the granulosa-cell tumor and the theca-cell tumor. There are two other ovarian endocrine tumors which produce masculinizing hormones. These tumors are the arrhenoblastoma and the masculinovoblastoma (hypernephroma) of the ovary. As might be expected, the masculinizing tumors are very rare. The arrhenoblastoma is believed to arise from rests of male-directed cells remaining from the early embryonic undifferentiated stage of the ovary. The masculinovoblastoma has been presumed to arise from adrenal rests in the ovary.

Granulosa-Cell Tumor.—The granulosa-cell tumor is the commonest ovarian endocrine neoplasm, estimated to comprise 10 per cent of solid ovarian carcinomas. Occurring at any age, it is characterized by production of excessive estrogenic hormone. In the child this causes precocious sexual changes, with development of the breasts and onset of menstruation. These changes of precocious puberty disappear following removal of the tumor. During the reproductive period, the tumor may cause either excessive menstrual bleeding or periods of amenorrhea. After the menopause, the hyperestrinism causes resumption of menstrual bleeding. Endometrial hyperplasia is present in these cases as the result of the excessive estrogen.

Most granulosa-cell tumors are benign or of very low-grade malignancy, so that complete removal results in cure. Ten per cent or more are malignant and form metastases. The origin of these tumors is believed to be from either (1) embryonal rests of granulosa cells (progranulosa cells of ovarian mesenchyme) or (2) granulosa cells of the follicle.

Granulosa-cell tumors are unilateral, circumscribed tumors, with a smooth or slightly nodular surface, and a few millimeters to 30 centimeters in diameter. The cut surface shows

a fleshy, pale yellow or grayish tissue, sometimes with cystic areas. Gross features alone are not characteristic enough for diagnosis.



Fig. 268.—Granulosa-cell tumor of ovary, folliculoid type.

Histologic structure is widely variable, both in different specimens and in the same tumor. The main types are folliculoid, cylindromatous, and diffuse. In the folliculoid type there is formation of follicle-like structures, sometimes with

surrounding stroma. Call-Exner bodies (see p. 560) may be seen. The **cylindromatous** form has solid cords and strands of tumor cells separated by a small amount of fibrous stroma. In the **diffuse** variety there may be solid, sarcoma-like, patternless masses of tumor cells. Areas of luteinization are not uncommon, and when this is predominant, the designation "luteoma" has sometimes been used. Lipoid-containing fibromatous areas such as characterize theca-cell tumor also may occur, indicating their close relationship. Adenocarcinoma of the uterus has been observed to be quite frequent in association with granulosa-cell and theca-cell tumors of the ovary.²⁹ This suggests hyperestrinism as a possible contributing etiologic factor in endometrial carcinoma, although final proof is lacking.

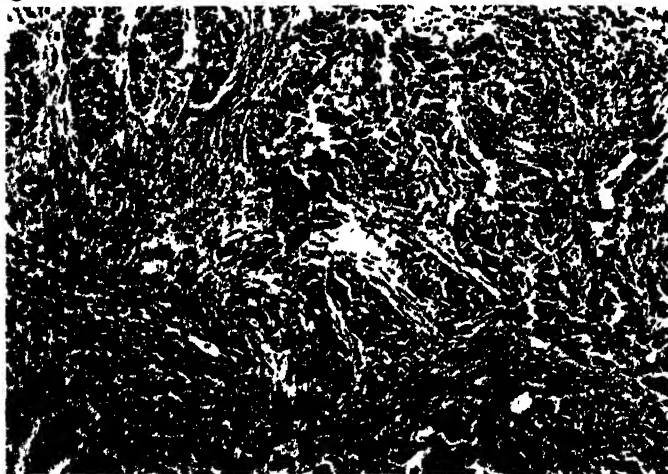


Fig. 269.—Granulosa-cell tumor of ovary, cylindromatous type.

Theca-Cell Tumor (Thecoma).—Theca-cell tumors are often considered as a type of granulosa-cell tumor, but usually theca-cell tumors present distinctive morphologic features which warrant separate consideration. Rarer than granulosal tumors, these fibromatous neoplasms have a later age incidence and are characterized by a content of doubly refractive lipoid (cholesterol). Excess production of estrogenic hormone results in irregular uterine bleeding with endometrial hyperplasia. In rare instances the tumor is malignant and has the character of a spindle-cell sarcoma.

Grossly they are unilateral, solid, encapsulated tumors, of firm consistency, and in general quite like the more common ovarian fibroma. The cut surface shows a yellowish fibrous tissue structure. Histologically of fibromatous appearance, they have bundles of broad spindle cells which irregularly interlace. Doubly refractive lipid within tumor cells and in surrounding connective tissue is the diagnostic feature.

Arrhenoblastoma.—Arrhenoblastoma is a rare solid ovarian tumor which by hormone production causes loss of feminine characteristics and masculinization. It is thought to arise from rests of male-directed cells persisting from early stages of gonadal development. Most of these tumors occur between puberty and the menopause and exhibit moderate malignancy. Defeminizing changes of amenorrhea, sterility, and atrophy of breasts are followed by development of the masculine characteristics of hirsutism, deepening of voice, and enlargement of the clitoris. Clinical differentiation must be from other causes of masculinization, such as adrenal cortical tumors. Arrhenoblastomas vary greatly in their degree of hormonal activity.

Grossly they are small or of moderate size, gray or yellowish, firm, and unilateral. Microscopically, there is wide variation in appearance, with highly differentiated, intermediate, and undifferentiated varieties. The more undifferentiated types have the most marked clinical masculinization. The most differentiated type (testicular tubular adenoma) shows a pronounced tubular arrangement closely imitating the testicle. The undifferentiated type consists of sheets and masses of cells having a sarcomatous appearance. In the intermediate grades there are varying degrees of imperfect attempted tubule formation. An arrangement resembling sex cords and areas having cells similar to the interstitial (Leydig) cells of the testis may be present. The tumor usually contains considerable lipid.

Gynandroblastoma.—Ovarian tumors have been described which give rise to both masculinization and evidences of hyperestrinism. The secondary sexual characters change in a male direction, but with continuation of cyclic menstrual bleeding. The microscopic pattern in such cases is not constant, but usually presents combinations of the features found in arrhenoblastomas and granulosa-cell tumors. It has been suggested that gynandroblastomas are of teratomatous nature.²⁰

Masculinovoblastoma.—Masculinovoblastoma (adrenal tumor of the ovary) is a rare tumor which produces masculini-

zation with clinical effects similar to those of the arrhenoblastoma. While its probable origin is from rests of adrenal cortical tissue in the ovary, another possibility is that it

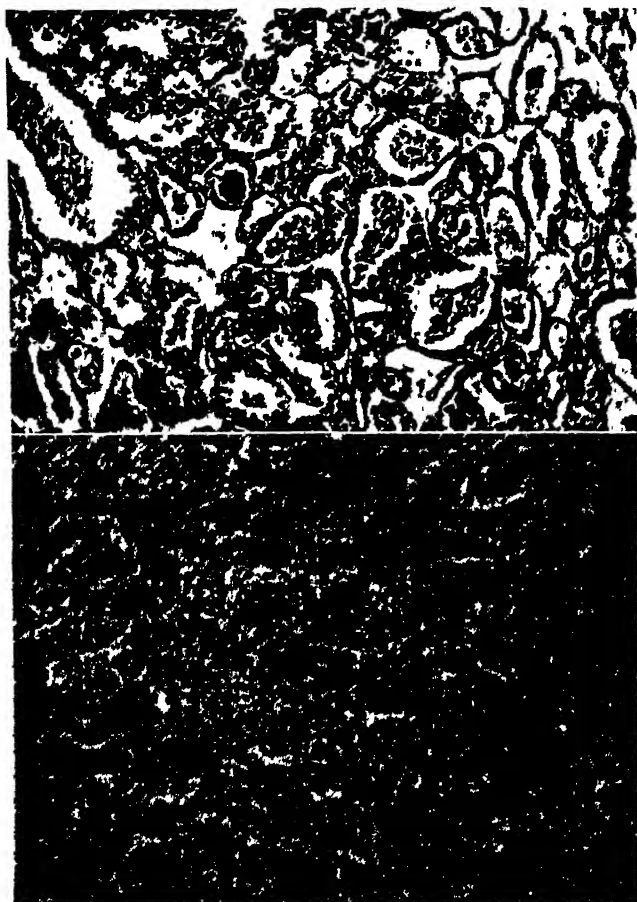


Fig. 270.—Arrhenoblastoma of the ovary. The upper figure shows the tubular adenoma type.

may arise from luteal cells. It is unilateral, of small or moderate size, an orange-yellow color, and high fat content. Microscopically it is composed of large pale cells similar to those of adrenal cortex.²¹ Hypernephroid tumors of the

ovary, similar to the clear cell adenocarcinoma of the kidney, also occur. These yellow malignant tumors do not produce masculinization.²²

THE FALLOPIAN TUBES

The fallopian tubes have a muscular wall covered on the outer surface by peritoneum, and lined by a mucosa which is thrown up into intricate papillary arborescent folds. Some of the cells lining the mucosa are ciliated, while others are nonciliated and appear to have a secretory function. The tubal epithelium undergoes some cyclical changes with the menstrual cycle. During menstruation or pregnancy, the epithelial cells are low or flat. A few days after menstruation the epithelium becomes tall, columnar, and compact. After ovulation the ciliated cells become lower, and the lining epithelium appears flattened and irregular or uneven. Activity of secretory cells becomes more prominent and in later parts of the cycle they too become lower.¹

Salpingitis.—Inflammation is the most common tubal lesion. In 60 to 80 per cent of cases this is due to gonococcal infection. Streptococcal or staphylococcal infection of the tube is commonly due to post-abortal or post-partum spread from an infected uterus. Less than 5 per cent of cases of salpingitis are tuberculous.

The gonococcus reaches the tubes from an infection of the cervix, spread by way of the endometrium. In acute salpingitis the tube is swollen, reddened, and has a purulent exudate in the lumen. Microscopically, the mucosal folds are enlarged, edematous, and diffusely infiltrated by polymorphonuclear leucocytes. Later this inflammatory exudate also involves the muscularis and serosa of the tube. The fimbriated extremity may become adherent to the ovary and extension of the infection to the ovary by way of a ruptured follicle produces a tubo-ovarian abscess. With subsidence of the inflammation to a subacute phase, a greater proportion of lymphocytes and plasma cells compose the exudate.

In the nongonorrheal acute salpingitis, there is greater enlargement of the tube, and the inflammatory infiltration is proportionately greater in muscular and serosal layers.

In chronic salpingitis the thickened mucosal folds are infiltrated by lymphocytes and plasma cells, and muscularis and serosa may be similarly involved. Adhesions may be present between mucosal folds and when marked result in a gland-like or follicular pattern (follicular salpingitis).

The lumen often becomes blocked by adhesions. The purulent exudate may accumulate and greatly distend the blocked tube into a large retort-shaped mass (pyosalpinx). Resorption of the exudate ultimately leaves the cavity filled with a watery fluid (hydrosalpinx). The mucosal folds may be very atrophic and flattened (hydrosalpinx simplex), or due to adhesions the folds may form a number of distended compartments (hydrosalpinx follicularis).

Salpingitis isthmica nodosa is a form of chronic salpingitis in which the medial portion of the tube is nodular. In most cases the nodules are due to diverticula of tubal epithelium, but some of the nodules may be inflammatory lesions without diverticulosis.²³ Microscopically, one sees marked thickening of the wall, and a number of small irregular lumina lined by mucosal epithelium. These epithelial-lined spaces must be distinguished from endometriosis and from tumor.

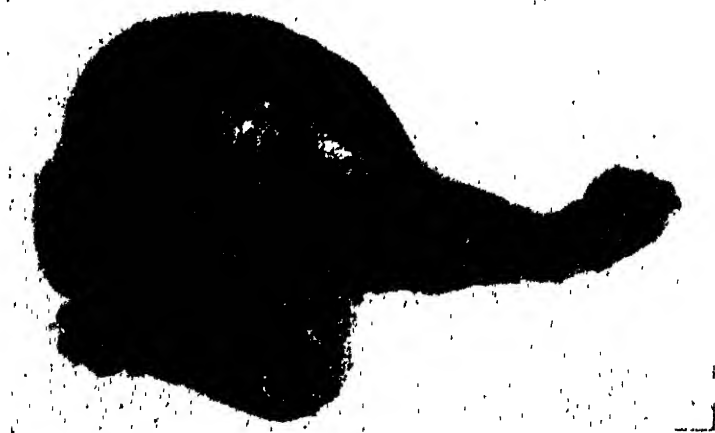


Fig. 271.—Hydrosalpinx. Note the retort-shaped deformity of the fallopian tube. (Courtesy Dr. H. C. Schmeisser.)

Tuberculous salpingitis is secondary to tuberculosis elsewhere, usually in the lungs, but is the primary site of tuberculosis in the female genitalia. From the tube spread often occurs to endometrium and to peritoneum. The microscopic appearance is similar to that of tuberculosis elsewhere, with epithelioid and giant cells, and caseation.

Tumors of the Fallopian Tubes.—Primary carcinoma of the tube is a rare lesion. The tube is greatly enlarged and

sausage-shaped. Microscopically it is usually a papillary carcinoma. Metastatic carcinoma of the tube is more frequent than the primary form and is usually from the ovary or uterus. Sampson has demonstrated the method by which implantation of such tumors may occur in tubal mucosa.²⁴

Tubal Pregnancy.—Ectopic pregnancy results when a fertilized ovum becomes implanted in any site other than the endometrium. In most cases the ectopic site is in a fallopian tube. An important factor causing tubal pregnancy is the effect of chronic salpingitis which prevents passage of the fertilized ovum into the uterus or delays it until the trophoblast is developed sufficiently for successful implantation. Chorionic villi penetrate the tubal wall. A decidua forms in the endometrium similar to that which would form if the implantation were in the uterus.

In most cases of tubal pregnancy, death of the ovum occurs in a few weeks. Tubal rupture is common. This may be internal, with bleeding into the tube (hematosalpinx) or external rupture into the abdominal cavity. In the latter case bleeding is usually profuse and sometimes fatal. Tubal abortion occurs when the ovum breaks away and is expelled from the tubal orifice. This usually causes hematosalpinx and often profuse bleeding into the abdominal cavity also. Tubal pregnancy is the commonest cause of hematosalpinx. When the ovum dies, the uterine decidua may be discharged as a thick cast.

THE UTERUS

The uterus has a thick muscular wall, the myometrium, and a lining layer, the endometrium, composed of glands set in a connective tissue stroma. The main portion is the corpus or body of the uterus, while the smaller lower part, the neck or cervix of the uterus, protrudes into the upper part of the vagina. The cervical lining layer also contains glands, though distinctive from those of the body of the uterus, and surrounds a narrow canal. The portion of cervix which protrudes into the vagina is covered by squamous epithelium.

The uterus undergoes remarkable hypertrophic changes during pregnancy, followed after delivery by normal regressive and atrophic changes. One of the most serious complications of this process is infection, i.e., a puerperal endometritis and myometritis, which in severe cases may spread widely by lymphatics and veins.

The endometrium undergoes cyclic changes under the influence of ovarian hormones. These changes are in preparation for implantation of a fertilized ovum, and failing this, culminate in menstruation. Ovarian endocrine imbalance may disturb the endometrial cycles, so that pathologic hyperplasia or other abnormalities result. Tumors arising from the endometrium are most commonly adenocarcinomas. Endometritis is most often due to abnormal retention of placental tissue, but tuberculous endometritis not uncommonly follows tuberculous salpingitis. Ectopic endometrial tissue (endometriosis) is quite frequent in various situations in the pelvis. Most commonly the misplaced islands of endometrium are in the muscular wall of the uterus, the condition here being termed adenomyosis.

The chief lesion of the myometrium is a benign tumor of smooth muscle and connective tissue, termed a fibromyoma or "fibroid." These tumors are extremely common, particularly in the Negro race, are often multiple, and reach large sizes. A small proportion undergo sarcomatous change.

Endometrium

Pathologic disturbances of the endometrium include abnormalities of the cyclical hormonal changes, inflammation, tumors, and ectopic endometrium (endometriosis).

Cyclical Changes.—The cyclical changes are controlled by the ovarian hormones of the maturing follicle (estrogen) and the corpus luteum (progesterone). The estrogenic effect is essentially to stimulate proliferation of endometrial glands. Progesterone promotes a secretory activity of the glands, and a decidua-like change in the stromal cells. If pregnancy fails to occur, the corpus luteum degenerates, and there is a breakdown of the endometrium with hemorrhage and sloughing of all except the most basal layer (menstruation). Thus there are three main phases in the menstrual cycle: (1) the proliferative (fifth to fourteenth day of cycle) controlled by estrogen, (2) the secretory (fifteenth to twenty-eighth day) in which progesterone as well as estrogen influences the endometrium, and (3) the menstrual (first to fourth day). The beginning of the cycle is counted from the first day of menstruation, since that is a point most easily determined. Ovulation usually occurs near the middle of the cycle (fourteenth day) and is followed shortly by corpus luteum formation and a progesterone effect on the endometrium. The histologic changes are summarized in Table XVI.

TABLE XVI
HISTOLOGY OF THE MENSTRUAL CYCLE

DAY OF CYCLE	OVARY	ENDOMETRIAL PHASE	ENDOMETRIAL HISTOLOGY
1 to 4	Degenerating corpus luteum	Menstrual	Infiltration of leucocytes, degeneration and breakdown of endometrium; hemorrhage and sloughing of endometrium
5 to 12	Developing follicle Mature follicle	Proliferative (estrogen)	Regeneration of endometrium from basalis. Glands rounded, regular, with piled-up cells; mitoses; stromal cells elongated, spindle with scanty cytoplasm
13 to 15	Ovulation		
16 to 28	Corpus luteum	Secretory (estrogen + progesterone)	Glandular epithelium lines up in single layer; subnuclear vacuolization, followed soon by peripheral vacuolization of glandular epithelium with basal nuclei; glands tortuous, saw-toothed; stroma edematous in early stages, later stromal cells swollen, rounded, finally decidua-like; congestion of blood vessels and infiltration of polymorphonuclears and lymphocytes in final stages

During the menstrual phase (first to fourth day) there are degeneration and breakdown of the endometrium, with thrombosis of blood vessels and infiltration of leucocytes. Except for a basal layer the endometrium is desquamated. From the remaining basal tissue there is rapid regeneration. The basal layer does not participate in the histologic changes of the cycle.

The proliferative phase (fifth to fourteenth day) extends from the end of menstruation to ovulation and is controlled by estrogen from the developing ovarian follicle. It is characterized by active proliferation of cells and formation of straight tubular glands. At first the endometrium is 1 to 2 mm. in thickness and contains 3 or 4 glands per low-power field, set in a loose stroma. The lining epithelial cells are columnar, have nuclei at all levels, and are crowded together or "piled-up." In the latter part of this stage, mitoses may

be numerous in the glands. The glands in this phase appear very regular in outline, and either elongated or round, depending upon the direction in which they have been sectioned. Toward the end of this phase, the nuclei of the glandular cells are basal in position, and the cells become longer. The average number of glands now may be 6 or 7 in a low-power field, and the endometrium is 2 to 2.5 mm. in thickness. The stromal cells are elongated, spindly, and have scanty cytoplasm.

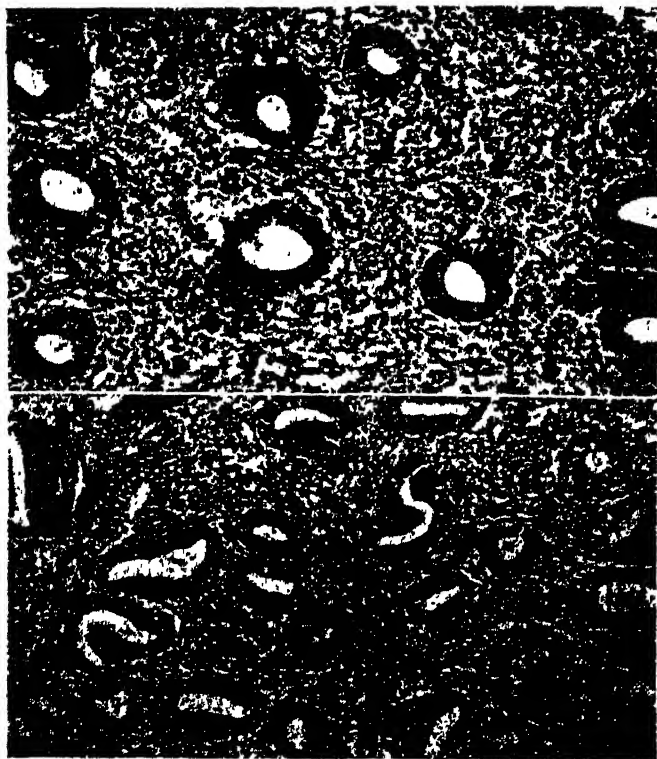


Fig. 272.—Endometrium in proliferative phase. The rounded and regular glands are lined by several layers of cells.

The secretory (differentiative or progestational) phase (fifteenth to twenty-eighth day) extends from ovulation to the beginning of menstruation. Its characteristic features are the effect of progesterone produced by the corpus luteum.

Hence when these changes are present, ovulation may be assumed to have occurred. The main features are tortuosity of the glands, evidence of secretory activity, and in later days of the phase a swelling and rounding up of the stromal cells so that they resemble decidual cells.

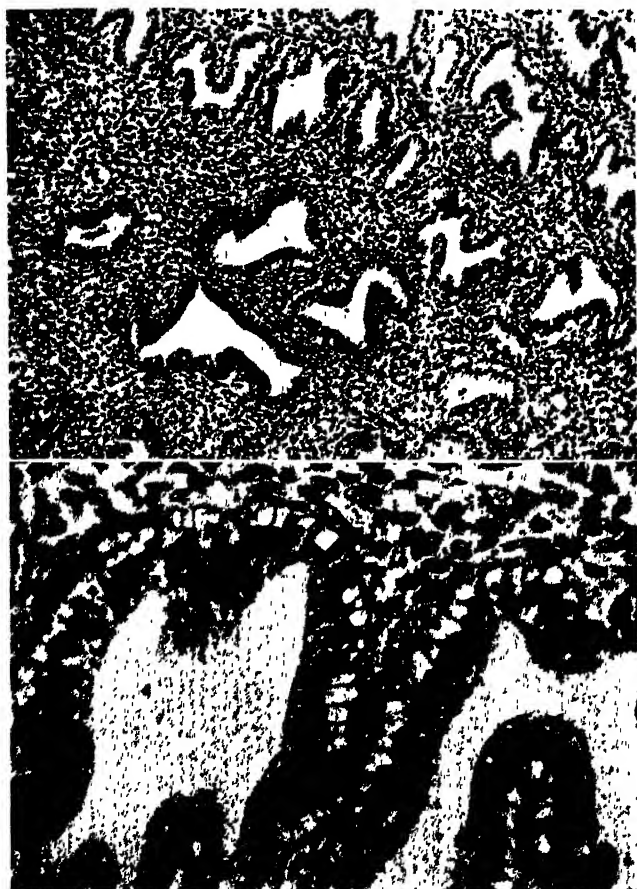


Fig. 273.—Endometrium in early secretory phase. The subnuclear vacuolization is a characteristic feature.

Early in the secretory phase the columnar glandular cells become more regularly arranged into line, no longer appearing "piled up." Clear vacuoles of glycogen appear at the

base of the cells, pushing the nuclei into a more central position. This subnuclear vacuolization is one of the important early indications of this phase. It is soon followed by vacuolization of peripheral parts of the cells and sinking of the nuclei to a basal position. The glands become twisted and have a very irregular, saw-toothed appearance. In early days of this phase the stroma is loose and very edematous, particularly in its central portions, so that a spongy layer may be distinguishable between a lining compact layer and the basal portion. Late in the phase the stromal cells become swollen and rounded, possess abundant cytoplasm, and are young decidual cells. The endometrium at this time may be 4 to 7 mm. in thickness. The blood vessels are congested, and there may be small hemorrhages. At the end of this phase there is an infiltration of polymorphonuclear leucocytes and lymphocytes in the stroma.^{25, 26, 27}

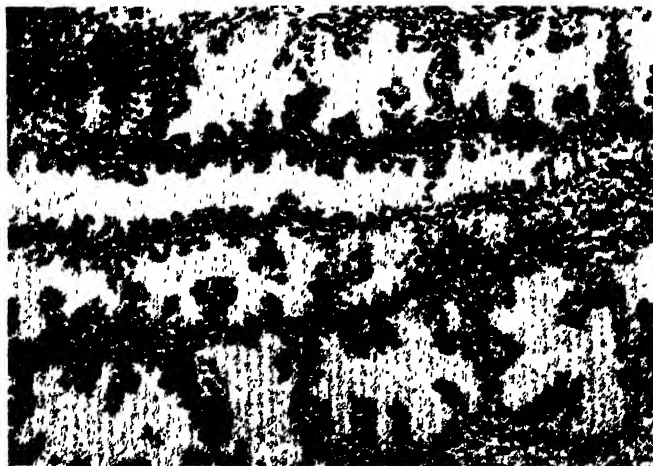


Fig. 274.—Endometrium in secretory phase. Note the irregularity of the glandular linings.

Endometrial Hyperplasia.—Cystic glandular hyperplasia of the endometrium is an exaggeration of the changes of the proliferative phase of the menstrual cycle. It is due to excessive estrogen production, either absolute or relative, because of failure of ovulation and corpus luteum formation. Follicular retention cysts are usually present in the ovaries. Most cases occur after the age of 35 years, and it is most common around the menopausal period. Its chief symptom is

irregular and persistent bleeding (functional uterine bleeding). The bleeding is believed to occur when there is a sharp drop or withdrawal of estrogenic hormone, and hence it is not correlated with the degree of hyperplasia, nor is it a regular and invariable accompaniment. Endometrial hyperplasia also accompanies tumors having excess estrogenic hormone production, such as granulosa-cell and theca-cell tumors. During reproductive years, it is a benign lesion, but after the menopause endometrial hyperplasia may predispose to adenocarcinoma.²⁸

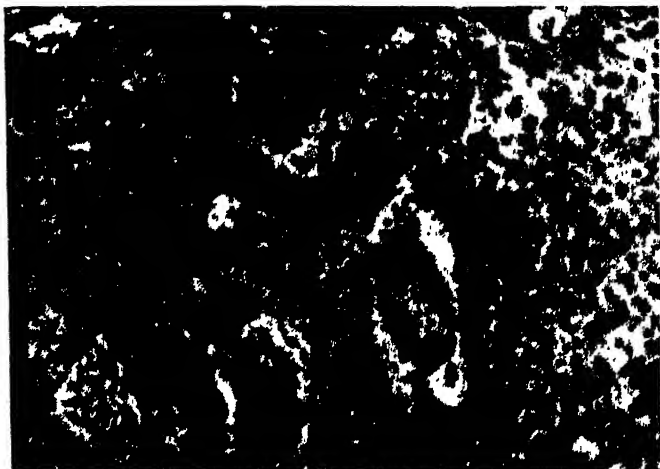


Fig. 275.—Decidual change in endometrial stroma.

The hyperplastic endometrium is thickened, velvety, and often roughened by folds or irregular polypoid projections. Curettage produces abundant endometrial fragments which are firm, smooth, intact, non-necrotic and nonfriable, and hence usually distinguishable grossly from the abundant but friable and necrotic masses obtained when there is carcinoma of the uterus.

Microscopically the endometrium has the features of proliferative endometrium, with the addition of marked irregularity in size of the glands. Some glands are small, some medium-sized, and others show cystic enlargement. When the latter are abundant, the endometrium has a characteristic "Swiss cheese" appearance. Proliferative activity (mitoses) is sometimes evident in the stroma as well as in the glandular

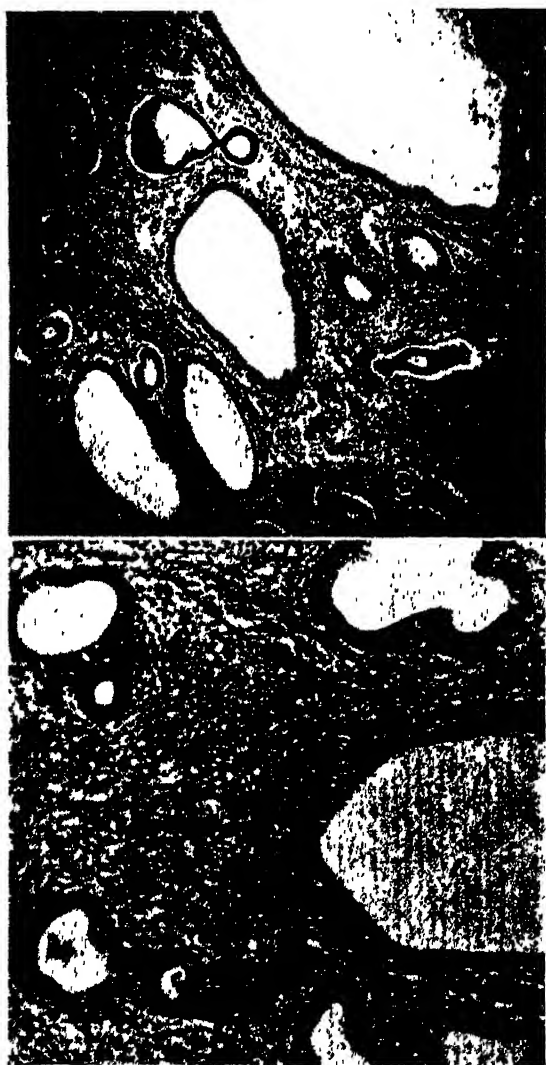


Fig. 376.—Endometrial hyperplasia. “Swiss cheese” appearance due to cystlike dilatation of endometrial glands.

epithelium. The endometrium appears similar at all levels, without layering. Small focal areas of degeneration and necrosis, with thrombosis of small vessels, are sometimes present.

Endometrial Polyp.—Endometrial polyps are localized areas of benign overgrowth of endometrium, attached by a narrowed pedicle or base. Endometrial hyperplasia may be polypoid in form, but polyps also occur singly and without generalized endometrial change. They may undergo cyclical changes with the rest of the endometrium, but often they show a proliferative type of change only, with cystic glandular dilatation and a picture similar to endometrial hyperplasia. Large polyps often ulcerate and bleed or show considerable inflammation. Malignant change in a polyp is uncommon.

Endometritis.—Inflammation of the endometrium may be due to puerperal infection (streptococcus, staphylococcus, etc.), gonorrhea, or tuberculosis. The most severe form is the acute puerperal infection, which is often associated with myometritis, infective thrombophlebitis, and lymphangitis. Hence the infection may spread throughout the pelvis and to other parts of the body. Gonococcal endometritis is usually less important than the tubal and cervical inflammation. Tuberculous endometritis is secondary to tuberculosis of the Fallopian tube and shows the usual microscopic picture of epithelioid and giant cells. Postabortive endometritis is commonly seen in curettings sent to the laboratory and is identified by finding remnants of retained chorionic villi.

Endometriosis.—Endometriosis refers to the condition of ectopic endometrium, or endometrial tissue in an abnormal position. The most common abnormal site is the muscular wall of the uterus, there having been direct invasion of myometrium. Here the condition is termed adenomyosis or internal endometriosis. Other common sites are ovary, fallopian tube, or peritoneal surfaces any place in the pelvis. Occasionally the condition involves laparotomy scars or the umbilicus.

There are two main theories regarding endometriosis, neither of which satisfactorily explains all cases. Sampson presented evidence that it is due to retrograde menstruation, i.e., viable fragments of endometrium which pass through the fallopian tube at the time of menstruation and implant on serosal surfaces. The second theory is that it is due to coelomic heteroplasia, i.e., an abnormal differentiation of certain areas of coelomic epithelium. The serosal cells of the peritoneum and the mucosa of the uterus, tubes,

and vagina have a common origin, and some hormonal factor may stimulate the metaplasia in extrauterine sites. Adenomyosis appears to be best understood as an exaggerated invasiveness of the endometrium. There is usually a direct continuation of the uterine mucosa with the endometrial areas in the myometrium.

The extrauterine endometrial masses are usually small cysts, often only a few millimeters in diameter, containing a thick chocolate-like fluid and possessing a hemorrhagic lining. In the ovary these chocolate cysts may be several centimeters in diameter but in rare cases are very large. They are easily confused with hemorrhagic corpus luteum cysts. When endometrial implants of pelvic peritoneum are numerous, they cause considerable irritation and development of pelvic adhesions. The aberrant endometrial tissue may respond to ovarian hormonal stimuli with periodic "menstrual" bleeding. Hence the cystic dilatation by accumulation of chocolate-colored hemorrhagic material. Rupture of the cysts causes peritoneal irritation, fibrosis, and adhesions.

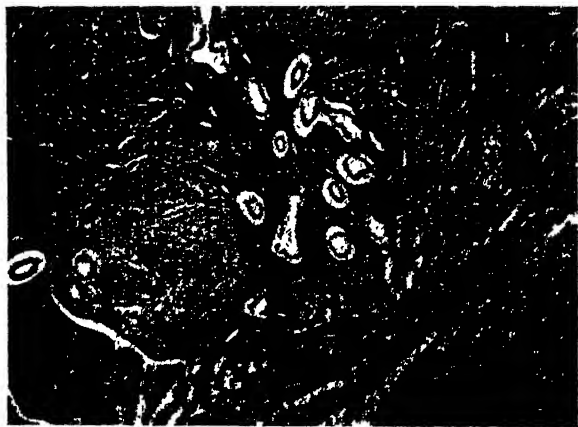


Fig. 277.—Adenomyosis (endometriosis) of wall of uterus. Islands of endometrial glands and stroma surrounded by myometrium.

Identification of endometriosis depends on microscopic recognition of endometrial glands and stroma. In the larger endometrial cysts, as in the ovary, this may be difficult due to atrophy of much of the endometrial lining. The symptoms caused by endometriosis are often those of chronic pelvic inflammation, although dysmenorrhea may be prominent.

Tumors of the Corpus Uteri

Tumors arising from the body of the uterus include:

1. Fibromyomas (fibroids) arising from the myometrium, and which occasionally by malignant change result in sarcoma;
2. Adenocarcinoma arising from endometrial glands, and its rare variant, adenoacanthoma;
3. Sarcoma derived from endometrial stroma;
4. Mixed tumors of mesodermal origin, and
5. Hydatidiform mole and chorionepithelioma, which respectively are due to cystic degeneration and malignant change in chorionic villi.



Fig. 278.—Fibromyoma of uterus with degenerative changes. (From South. M. J. 31: 968, 1938.)

Fibromyoma (Myoma, Fibroid).—The commonest tumor of the uterus is a benign smooth muscle growth of the muscular wall. It occurs during the reproductive age and tends to regress after the menopause, whether artificial or induced. It is said to occur in 20 per cent of women over 35 and has a much higher incidence in the Negro race. The tumors are frequently multiple, grow to large size, and are subject to degenerative changes on account of their poor blood supply. They distort the uterus, have secondary effects on the endometrium, and interfere with pregnancy and delivery. A small proportion become malignant.

ETIOLOGY.—The etiology of uterine myomas is not known, though a relationship to hyperestrinism has been postulated. Evidence for this is incomplete. Sterility is quite common with fibromyomas, probably as an effect rather than a cause.

GROSS APPEARANCE.—Most fibromyomas involve the body of the uterus, but a troublesome small proportion are in the cervix. The tumors begin in the myometrium as **intramural** growths. With continued expansive growth they may take up a position beneath the peritoneum (**subserous** fibroids) or beneath endometrium (**submucous** fibroids). In either case they can become pedunculated and attached by a narrow pedicle or neck which carries their blood supply, and which is easily twisted. **Intraligamentous** fibroids are those which extend out between layers of the broad ligament. In rare cases the omentum becomes adherent to a pedunculated fibroid and provides a new blood supply. The uterine attachment may be lost, and it becomes a **wandering or parasitic** fibroid. The tumors are always well circumscribed and easily shelled out from their surrounding pseudocapsule. Usually multiple, they vary in size from a few millimeters to enormous growths many centimeters in diameter and weights up to 100 pounds have been reported. On being cut a fibroid tends to bulge outward due to retraction of surrounding myometrial tissue. The cut surface is firm and has a characteristic whorled, trabeculated appearance due to interlacing bundles of muscle fibers.

MICROSCOPIC APPEARANCE.—Microscopically the bundles of smooth muscle cells can be seen running in all directions and producing the whorled pattern. When cut longitudinally, the muscle cells are spindle shaped, with elongated rod-like nuclei. When the bundles are cut across, the cells appear rounded with central round nuclei. The fibrous stroma may be slight but is variable in amount. Mitoses are rare, and there is but little variation in the size, shape, and staining properties of the cells.

DEGENERATIVE CHANGES.—Degenerative changes in fibroids are very common, due mainly to their poor blood supply. These secondary changes include hyaline degeneration (most common), necrosis and red degeneration, calcification, and cystic degeneration. Telangiectatic and fatty changes occur but are unusual. Infection of a fibroid is most common in the submucous type. Sarcomatous change affects but a small proportion of fibroids (probably less than 2 per cent) and

often may be suspected grossly when the cut surface of the tumor is soft, white, and brain-like in consistency and appearance.

EFFECTS.—The more important effects on the uterus are caused by the interstitial and submucous fibroids. They may result in great distortion of the uterus and its cavity, so that growth and accommodation of a fetus or its delivery may be impossible. With submucous fibroids the overlying endometrium becomes thin and atrophic. Infection, endometrial inflammation, and sometimes bleeding result from submucous growths.

Adenocarcinoma of the Uterus.—Carcinoma of the body of the uterus is an adenocarcinoma arising from endometrial glands. It comprises about 10 per cent of uterine carcinomas, being much less common than carcinoma of the cervix. Its peak incidence is after the menopause, at about 55 years. The chief symptom is post-menopausal bleeding, the diagnosis being made, except in advanced cases, by curettage and microscopic examination of tissue fragments. Post-menopausal hyperplasia of the endometrium appears to have some relationship to development of adenocarcinoma.²⁸

GROSS APPEARANCE.—The tumor may involve the endometrium diffusely, making it thick, rough, and polypoid, before there is much myometrial invasion. The tumor tissue tends to be bulky, friable, and often with areas of necrosis. In other cases the tumor tissue is localized to one part of the fundus and may be polypoid in form.

MICROSCOPIC APPEARANCE.—Microscopically, there is usually a well-differentiated glandular structure, but with marked irregularity and lawlessness of pattern. Often the glands are closely and irregularly placed, with little stroma between them. Actual invasion through basement membranes may not be seen except in the more malignant examples. The cells show varying degrees of differentiation. There may be marked variation in size, shape, and staining of cells and many typical and atypical mitoses in the highly malignant types. Histologic grading, on the basis of the proportion of differentiated and undifferentiated cells, is into four groups according to the method of Broders (see p. 204) and gives some indication of prognosis.

SPREAD.—Spread of adenocarcinoma of the uterus is chiefly by lymphatics to involve the lumbar glands at the lower end of the aorta, and sometimes the inguinal glands. There is a variable degree of direct invasion of the myometrium, and extension to the cervix occurs readily. In some cases there

is implantation on tubes, ovaries, or peritoneum. Blood vessel spread is a late event.

ADENOACANTHOMA.—Adenoacanthoma of the uterus is an uncommon type of adenocarcinoma in which there are areas of benign squamous epithelium among the gland-forming tumor cells. The squamous metaplasia is from certain "in-different" cells beneath the columnar epithelium which possess the ability to form squamous epithelium.¹

Sarcoma of the Uterus.—Sarcoma of the uterus is relatively uncommon, constituting about 3 per cent of uterine malignancies. It is most common during the fourth and fifth decades. Sarcoma may arise from fibromyomas or from muscle or connective tissue elements of the uterus. Its symptomatology does not easily distinguish it from other uterine malignancies.

The gross appearance may suggest the diagnosis but often is not distinctive. In malignant myomas the firm consistency and whorled appearance of fibroids are lacking, and the tissue is soft, rubbery, and fleshy. Endometrial sarcoma is often polypoid.

Microscopically the tumor may be a spindle cell, round cell, or mixed type. The degree of malignancy rather accurately parallels the number of mitoses.³⁰ Metastasis is mainly by blood stream to the lungs and liver, and to a lesser extent by direct extension and lymphatics.

Mesodermal Mixed Tumors.—The rare mixed tumors of the uterus are probably due to inclusion and persistence in the Müllerian organs of mesenchymal cells which have a capacity for differentiation into various mesodermal tissues. Most cases arise in the body of the uterus and occur about the fifth decade. Those arising in the cervix occur at an earlier age. A grape-like type, sarcoma botryoides, involves particularly the upper vagina and occurs almost exclusively in infancy. The mesodermal mixed tumors are highly malignant and have a poor prognosis.

The growth begins in the mucosal layer and assumes a polypoid form. While not clinically distinctive, it is very constantly manifested by a sanguineous discharge from the vagina. Portions of the tumor are sometimes passed per vaginam.

Various types of tissue occur in these tumors, but myxomatous tissue and cartilage are most constant. Striated muscle fibers are frequent constituents. Myxosarcomatous and undifferentiated sarcomatous elements also are common.³¹

Hydatidiform Mole and Chorionepithelioma.—These tumors arise from fetal membranes, rather than from the tissues of the mother, but have the ability to invade and



Fig. 279.—Hydatidiform mole. Note the projecting grape-like vesicles which compose the mass. (Courtesy Dr. H. C. Schmeisser.)

destroy maternal tissues extensively. Determination of the degree of malignancy and prognosis from microscopic examination is a difficult procedure with many pitfalls.

The normal chorionic villus is covered by two layers of trophoblastic cells. The inner layer of Langhans cells is composed of cuboidal cells with a pale nucleus and cytoplasm. The outer or syncytial layer consists of masses of cytoplasm having multiple very dark nuclei. These trophoblastic cells

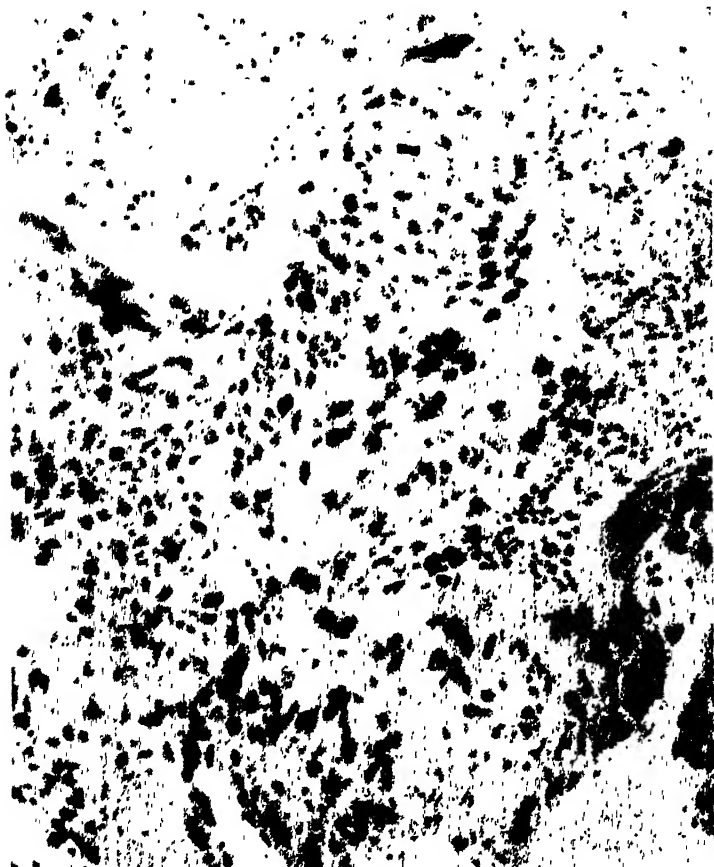


Fig. 280.—Chorionepithelioma.

are normally invasive, and even in normal pregnancy may be found invading myometrium and even blood vessels, and some cells may be carried to the lungs, but always regress and disappear. This normal invasive property may cause confusion in diagnosis, being mistaken for malignant invasion. The

benign invasion (infiltration with syncytium only) is sometimes called **syncytial endometritis** or **syncytioma**.^{32, 33}

Hydatidiform mole is a hydropic degeneration of chorionic villi, which become enlarged into clusters of grape-like vesicles. Blood vessels are scanty, and there is some proliferation of trophoblastic cells. This abnormality is uncommon, and while it is benign, the patient must be carefully followed as some cases progress to malignant chorionepithelioma. Various gradations occur between the benign hydatidiform mole and the malignant chorionepithelioma.

Hertig³⁴ found some degree of hydatidiform degeneration of chorionic villi in two-thirds of spontaneously aborted pathologic ova, apparently due to absence or defectiveness of fetal circulation. The typical hydatidiform mole appears to be derived from a pathologic ovum in which the embryo was absent or defective, but which failed to abort at the usual time.

Chorionepithelioma is a very malignant and extremely rare tumor. There is massive overgrowth of both Langhans and syncytial cells, which exhibit many of the atypical features of malignant cells elsewhere. Invasion occurs freely in the pelvis, and blood stream spread occurs to the lungs and other organs. The ovaries are involved by multiple lutein cysts which reach a large size.

The biologic pregnancy tests (Aschheim-Zondek and Friedmann) are positive when living trophoblastic tissue is present in the body, and hence are often important in the diagnosis and management of hydatidiform mole and chorionepithelioma. Quantitative tests are even more useful than the ordinary qualitative procedures. It has been emphasized that spinal fluid gives a positive qualitative test in the presence of mole or chorionepithelioma, but not in normal pregnancy.³⁵

Chorionepithelioma also occurs in the male as a form of teratomatous tumor of the testis. Its microscopic features and malignancy are similar, and in such cases also the biologic pregnancy test is positive.

Pulmonary Embolism From the Uterus.—In addition to pulmonary embolism with placental fragments, there also may be widespread embolism of small pulmonary vessels by particulate matter found in amniotic fluid and by meconium. This may cause severe shock and pulmonary edema, coming on during labor or soon after its conclusion.³⁵

THE CERVIX UTERI

The cervix or neck of the uterus connects the vagina with the uterine cavity. It has an internal os, a canal lined with mucosa having high columnar epithelium and racemose glands, an external os, and a vaginal portion. At the external os there is a rather sharp line dividing columnar epithelium of the endocervix from the squamous epithelium which covers the portion which protrudes into the vagina. The main lesions of the cervix are inflammation (cervicitis), polyp formation, and carcinoma. Carcinoma of the cervix is a frequent and highly important tumor. In most cases it is a squamous-cell carcinoma arising from epithelium of the vaginal portion. Adenocarcinoma of the endocervix is uncommon, and when it occurs, it is often difficult to be sure that its origin has not been from endometrium.

Cervicitis

Acute cervicitis is commonly the result of gonococcal infection, though it may be caused by other organisms. **Chronic cervicitis** may be caused by traumatic or mechanical factors in addition to bacterial causes. It is one of the commonest gynecologic lesions and is the usual cause of vaginal discharge or leucorrhea. In chronic cervicitis the chief microscopic change is an infiltration of plasma cells and lymphocytes. **Erosion** of the cervix is a lesion in which there is an area of loss of the squamous covering of the cervix, and eventual replacement by columnar epithelium of the endocervix. This is to be distinguished from **ectropion** or eversion of the endocervical mucosa due to laceration of the cervix. In cervicitis inflammatory obstruction of the outlets of endocervical glands often results in their cystic dilatation (Nabothian cysts). **Epidermidization (squamous metaplasia)** is a common change in the cervix, particularly in the healing phase of erosions. Squamous epithelium invades beneath the lining of cervical glands, with a gradual lifting up and replacement of the cylindrical epithelium by squamous epithelium. This process is benign and is distinguished from carcinoma by the normal appearance of the squamous epithelial cells, the infrequency of mitoses, and the absence of invasion of interstitial tissues.

Tuberculous cervicitis is rare, and usually secondary to tuberculosis in the Fallopian tube. While the gross appearance may simulate carcinoma, the usual picture of tuberculosis is seen microscopically.

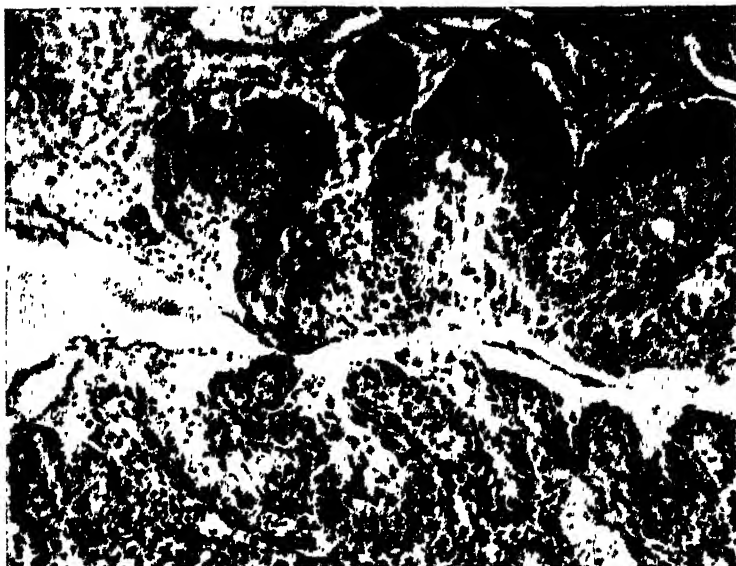


Fig. 281.—Squamous metaplasia in cervix. Squamous epithelial cells of benign appearance replacing glandular linings. (From Douglass and Faulkner: *Essentials of Obstetrical and Gynecological Pathology.*)

Cervical Polyp

In benign cervical polyp there is a localized overgrowth or heaping up of cervical mucosa, which becomes pedunculated and inflamed. It is often associated with inflammation of the cervix. Polyp tends to cause intermenstrual spotting or bleeding, and hence clinically it must be differentiated from carcinoma. Epidermidization is common in cervical polyps, but carcinomatous change occurs in very few.

Carcinoma of the Cervix

Carcinoma of the cervix is one of the most important and frequent forms of cancer affecting women. About 95 per cent are squamous-cell carcinomas, the remainder being adenocarcinomas arising from the cervical canal. The peak incidence is from 40 to 50 years, but many cases occur in the thirties. The most important factor in prognosis is the degree of extension when treatment is instituted, and secondarily the histologic grade of malignancy. Early cases

often are not distinctive grossly, so that early diagnosis depends on biopsy of suspicious areas. Spread is mainly by lymphatics.

ETIOLOGY.—Little is known concerning etiologic factors in cervical carcinoma. The chronic irritation of untreated lacerations from childbirth and other types of chronic cervicitis have been considered predisposing factors, but even these have been somewhat discredited. Certain types of leucoplakia are precancerous, or even early noninvasive carcinoma. Early cases have been recognized which exhibit characteristic cytologic changes of malignancy, but without invasion. They have been variously termed "precancerous," "noninvasive potential carcinoma," "carcinoma in situ," etc., and whether or not they have actually passed the borderline of malignancy is still debated.^{39 42} The lesion is probably similar to Bowen's preinvasive carcinoma of the skin (see page 634).

GROSS APPEARANCE.—The gross appearance of carcinoma of the cervix is not distinctive in early stages. It presents a small, hardened, granular or friable area at the margin of the external os. Later the tumor may grow outward, forming an everting growth of cauliflower appearance, or it may be inverting, extensively invading the cervix and vaginal wall, which are hardened and thickened. The Schiller test is of clinical value in bringing early suspicious areas into prominence when iodine is painted on the cervix. Normal cervical epithelium, due to its glycogen content, stains brown with iodine, whereas carcinomatous cells are deficient in glycogen and remain unstained.

MICROSCOPIC APPEARANCE.—Microscopically, the tumor is composed of squamous epithelial cells showing varying degrees of differentiation and atypicalness in their size, shape, staining reactions, polarity, and pattern. Invasiveness is evident except in the very earliest cases. Some keratin pearl formation may be present in the more highly differentiated examples.

GRADING AND PROGNOSIS.—In the cervix as elsewhere, the degree of malignancy of a tumor may be estimated from its growth activity and the immaturity or undifferentiation of the cells. The most commonly used systems of grading are those of Broders and of Martzloff. The features of these systems of grading are outlined in Table XVII.

The system of Broders is applicable in other situations as well and has been discussed on p. 204. The tumors are

TABLE XVII
GRADING OF CARCINOMA OF THE CERVIX

	BRODERS	MARTZLOFF	%
Least malignant Least radiosensi- tive	Grade I 0-25% undifferentiated cells 100-75% mature cells	<i>Spinal cell type</i> large mature cells, poly- hedral with definite cell outlines. Few mitoses. Keratiniza- tion may be present	16
Intermediate ma- lignancy Intermediate ra- diosensitivity	Grade II 26-50% undifferenti- ated cells 74-50% mature cells Grade III 51-75% undifferenti- ated cells 49-25% mature cells	<i>Transitional cell type</i> round nuclei, closely packed, indefinite cell boundaries	72
Highly malignant Most radiosensi- tive	Grade IV 76-100% undifferenti- ated cells 24-0% mature cells	<i>Spindle cell type</i> , deep staining — elongated nuclei, no definite cell boundaries, many mi- toses	12

classified into four grades. Grade I tumors have less than 25 per cent undifferentiated cells; grade II, 25 to 50 per cent undifferentiated; grade III, 50 to 75 per cent undifferentiated; and grade IV more than 75 per cent undifferentiated. The grades I and II tumors are less malignant and radio-sensitive, the grades III and IV more malignant and radio-sensitive.

Martzloff divided the tumors into three groups according to the predominant cell type, designated as (1) spinal cell, (2) transitional cell, and (3) spindle cell. In the least malignant *spinal cell type* the cells resemble those of the normal superficial layer of cervical squamous epithelium. The cells are large and polyhedral, have a large nucleus, abundant cytoplasm, and definite cell outline. These cells are relatively mature, and keratinization with epithelial pearls may be present. The *transitional cell type* is of intermediate malignancy and has the highest incidence. The cells resemble those of the middle layer of cells in the cervical squamous epithelium. They have rounded nuclei, often deeply staining, with little cytoplasm and indefinite cell outlines. The *spindle cell type* somewhat resembles the compact basal cells of squamous epithelium. This variety may have a sarcomatous appearance, the cells being elongated or spindle shaped, with dark-staining closely

placed nuclei, indefinite cytoplasm, and numerous mitoses. This type is most malignant and radiosensitive.

Histologic grading indicates rate of growth and degree of radiosensitivity but is probably less important in prognosis and as a guide to treatment than is the degree of extension of the tumor at the time examined. In this regard, certain stages of the disease have been designated as a guide.

Group I. Carcinomas limited to the cervix; the uterus is mobile. About 80 per cent obtain five-year cures.

Group II. Carcinoma spreading upward into uterus and downward into vagina; the uterus is partially mobile. About 40 per cent have five-year cures.

Group III. Carcinoma extending outward into the parametrium, with beginning fixation of the uterus. About 12 per cent have five-year cures.

Group IV. Carcinoma massively invading parametrium and extending to wall of pelvis, with complete fixation ("frozen pelvis"). No five-year cures.

Combined consideration of the histologic grade and the degree of extension leads to the most accurate prognosis.

A diagnosis of cervical or endometrial carcinoma can often be made by expert examination of a vaginal smear, but should be confirmed by biopsy or curettage.^{40, 41}

Extension and Metastasis.—Direct extension of cervical carcinoma occurs in a radial manner, and may massively involve the vagina and body of the uterus. Involvement of the parametrium may be by direct extension or by lymphatic permeation. Lymphatic extension is important, with metastasis developing in iliac and hypogastric nodes, and sometimes in sacral, obturator, lumbar, and inguinal nodes. In late stages there may be some blood stream spread. The cause of death is often obstruction in the urinary tract (e.g., blocking of ureters), leading to uremia, or hemorrhage due to erosion of a large vessel.

THE VULVA

The vulva, which includes structures from pubis to perineum, is subject to inflammatory lesions, atrophic changes, and tumors. Being covered by skin, the vulva is involved by the same inflammatory and neoplastic lesions as affect skin elsewhere. In addition venereal lesions occur frequently, including gonorrhea, syphilis, chancroid, lymphogranuloma venereum, and granuloma inguinale.

Venereal Lesions

Gonorrheal inflammation of the vulva affects particularly the urethra, the periurethral Skene's ducts, and Bartholin's glands. The squamous epithelium of adult vulvar and vaginal mucosa is resistant to gonorrheal infection, though the thin mucosa of infants is not. Bartholinitis is most commonly the result of gonorrheal infection, and in acute stages there is much swelling of the gland due to purulent exudate. In chronic phases there may be blockage of the duct, and cystic distension of the gland. Chronic gonorrheal infection may linger long in Skene's ducts and Bartholin's glands.

The primary chancre of **sypphilis** may involve the vulva, and in the secondary stage flat condylomas occur there (see p. 133).

Granuloma inguinale is a spreading ulcerative granulomatous lesion affecting the vulvar region. There is a subcutaneous infiltration of leucocytes, plasma cells, and characteristic large, foamy mononuclear cells which contain in their cytoplasm the encapsulated causative organisms, the Donovan bodies (see p. 149).

Lymphogranuloma venereum is due to a virus. Ulceration (esthiomene) and productive lesions (elephantiasis) involve the vulva, and spread occurs to pararectal lymphatics (see p. 151).

Kraurosis

Kraurosis is a shrinkage or atrophy of the vulva. A mild degree of such atrophic change is common after the menopause, but in kraurosis the change is extreme. It is probably due to withdrawal of ovarian hormones.

Leucoplakia

Leucoplakia of the vulva may be localized or may affect the whole vulva. It begins with hypertrophic changes in the epithelium, followed by atrophy and shrinkage. Chronic inflammatory cells are present in the subepithelial tissues. A collagenous layer develops beneath the epithelium, but there is absence of elastic tissue. The condition has associated serious symptoms, and there is a marked tendency to development of carcinoma.

Carcinoma

The most important tumor of the vulva is epidermoid carcinoma. It occurs in elderly women, usually after 60

years of age, and in about one-half of all cases is preceded by leucoplakia. The microscopic features are similar to those of epidermoid carcinoma elsewhere on the skin. There is early lymphatic extension to the superficial inguinal nodes, and later to deep inguinal, hypogastric, and iliac nodes, so that successful surgical removal is difficult.

In rare instances adenocarcinoma arises from Bartholin's gland. Hidradenoma of the vulva is a rare benign tumor of sweat gland origin. It is easily mistaken for adenocarcinoma (Fig. 282). Also rare are tumors of the clitoris, which have a more sarcomatous appearance.

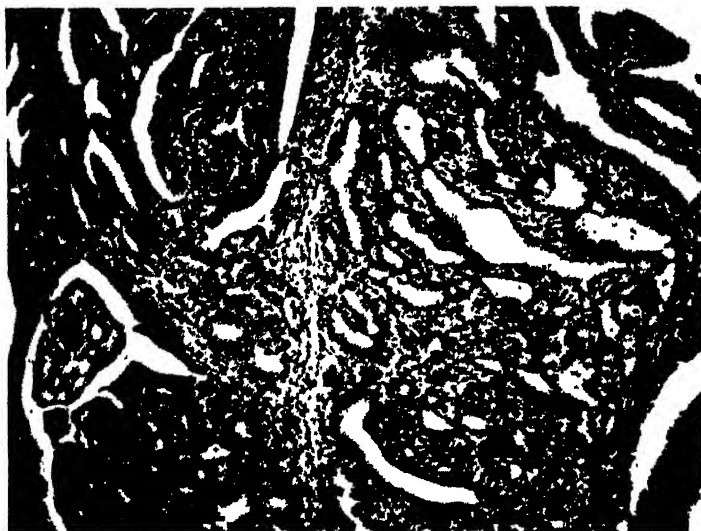


Fig. 282.—Hidradenoma of the vulva.

TOXEMIA OF PREGNANCY

The etiology of the toxemias of pregnancy (eclampsia, pre-eclampsia) is still uncertain. The main theories are that it is (1) a form of hypertensive cardiovascular renal disease, modified and colored by the metabolic disturbances of pregnancy, (2) an endocrine dysfunction, in which the pituitary plays the main part, (3) due to a toxic material absorbed from the placenta, particularly from areas of infarction. Whatever the exciting causes, changes in structure and function of the kidneys are constantly present.

Lesions are found in the kidneys, liver, placenta, and sometimes in other organs. The changes in the kidney have been described (see p. 312). Narrowing of capillary loops of glomerular tufts, mainly by thickening of the basement membranes, and degenerative changes in convoluted tubules are the usual findings.

The liver may show gross lesions which, while not constantly found, are so characteristic as to be diagnostic. Irregular large and small areas of hemorrhage may be evident on both the capsular and cut surfaces (see Plate IX, p. 382). Areas of hemorrhagic or anemic necrosis are common. Microscopically, there are hemorrhages and necroses of hepatic cells. These lesions are particularly in periportal areas, although any part of the liver lobule may be involved. The lesions have been attributed by some to thrombi in periportal venules. Diffuse degenerative changes are present in hepatic cells and sometimes destructive changes are so severe and widespread as to be classed as acute yellow atrophy.

Necrotic and hemorrhagic areas similar to those of the liver are occasionally found in other tissues, such as adrenal cortex. Areas of infarction very constantly occur in the placenta. The pituitary has been described as having increased numbers of basophiles, which may show hyaline degenerative changes. Basophilic invasion of the posterior lobe of the pituitary probably has no significance as far as eclampsia is concerned.

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CHAPTER XXII

THE BREAST

The breasts have an origin from the skin similar to that of sweat or sebaceous glands and like them are branched tubular glands. They are composed of a number of separated subdivisions, or lobes, each of which is drained by a duct. The various ducts come together and open at the nipple. The inner ends of the various ducts branch and rebranch, the beginning of the ducts being small glands or acini.

During fetal development and until about four months after birth the breast develops a duct system of 15 to 25 branching epithelial channels. Quiescence then follows until puberty, when there is renewed growth of the ducts. This developmental period is transient in males, and is followed by quiescence and involution. In females the ductal development continues during adolescence, and is accompanied by increase in the surrounding fibrous and fatty tissue, and by development of buds of cells at the ends of the tubules or ducts. Acinar structures differentiate from these buds under hormonal stimulation as sexual maturity is reached. With the occurrence of pregnancy and lactation, there is maximum acinar development. Proliferation of acinar buds appears to be a response to estrogenic stimulation, differentiation into acini is promoted by luteal hormones, and secretory activity is initiated by the pituitary. Throughout life the breast tissue is under the influence of pituitary and ovarian hormones. Mild cyclic changes involving hyperplasia followed by involution occur with each menstrual cycle. Luteal hormones influence epithelial hyperplasia in the breast in the latter part of the menstrual cycle. Regression occurs in the breast at the onset of the menstrual phase of the cycle, with involution and desquamation of epithelial cells, and infiltration of a few lymphocytes in the periglandular connective tissue.

During pregnancy the breast undergoes a tremendous proliferative activity. There is a great increase in number of glandular acini and relative decrease in connective tissue, apparently due to uninterrupted influence of luteal hormone. Following parturition, the placental hormone being withdrawn, secretory activity and lactation follow stimulation by the pituitary hormone, prolactin. The dense

glandular structure and hyperactive epithelium of the breast during pregnancy and lactation are a revelation of the power of physiologic hormonal stimulation. Following the menopause involutionary changes occur; connective tissue gradually replaces the glandular tissue, and the breasts decrease in size.

Pathologic changes in the breast consist of disturbances of the cyclic (hormonal) activity, the irritant effects of retained secretions, acute and chronic infections, and tumors.

Hypertrophy

Excessive development of the breasts is usually associated with endocrine disturbances. Hypertrophy in the male, gynecomastia, most commonly is associated with teratomatous tumors of the testicle, less often with tumors of the adrenal cortex or pituitary. Precocious puberty in female children usually has associated an excessive mammary growth, and

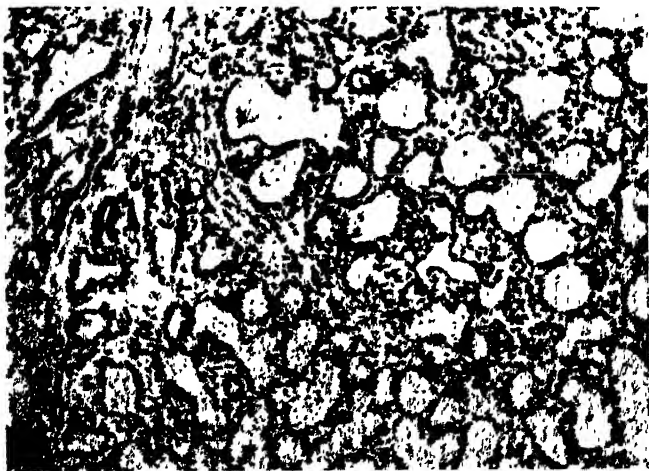


Fig. 283.—Lactating breast.

is found with granulosa-cell and theca-cell tumors of the ovary, adrenal cortical disturbances, and certain destructive lesions of the hypothalamus. Overgrowth of the breasts during adolescence (virginal hypertrophy) or during pregnancy (gravid hypertrophy) appears to be an excessive response to hormonal stimuli on the part of abnormally sensitive mammary tissue.

CHRONIC CYSTIC MASTITIS

Chronic cystic mastitis is a condition of diffuse or irregular proliferative change in the epithelium and connective tissue of the breast, often with cystic dilatation of the ducts. The term "chronic cystic mastitis," while deeply rooted, has evident defects in that the condition is not a chronic inflammation in the usual sense and is not always cystic. Numerous attempts at substitution of a more suitable name have resulted in a babel of nomenclature serving to confuse the subject greatly. The following terms referring to various phases of this condition may be encountered: fibrocystic disease, fibrocystic mastitis, cystic hyperplasia, chronic cystic mastopathy, Schimmelbusch's disease, mazoplasia, cystiphorous desquamative hyperplasia, cystoplasia, cystic disease of the breast, adenosis of the breast, and adenofibrosis.

Etiology.—The etiology of chronic cystic mastitis appears to be imbalance of hormones (estrogen and progesterone) influencing the breasts,^{1, 4, 5} or an irregular and abnormal response of the breast tissue to these endocrine influences. The irritative effects of retained secretions and desquamated material have been considered as another causative factor.

Mild degrees of the condition are very common, being usually a tender or painful area of breast tissue of increased density (mastodynia). The pain and swelling may be mainly premenstrual and due to vascular engorgement.⁵ There is stimulation to diffuse fibrosis and epithelial activity. In more marked cases the breasts are diffusely nodular or "shotty." Such nodularity is mainly due to epithelial hyperplasia, fibrosis, and microscopic cyst formation, and this stage has been referred to as "adenosis"¹ and "adenofibrosis."⁵ In a more advanced stage, one or more large cysts may result from secretory changes. Firm, freely movable masses varying in size up to several centimeters are sometimes palpable. When the nodularity is not diffuse, the condition must be distinguished from carcinoma. The age of greatest incidence is between 35 and 45 years.

Gross Appearance.—The gross appearance of the sectioned breast is often distinguished by the presence of cysts. Involved areas are grayish, of rubbery consistency, and not sharply outlined. The cysts may be of varying size and number, but they are not always present. The colorless content of the cysts shining through their tense, translucent walls gives them a bluish color (blue-domed cysts). Oc-

asionally the contents of the cyst are brown or yellow from altered blood pigment. The cut ends of dilated ducts may release casts of grayish desquamated material.

Microscopic Appearance.—The microscopic features consist of: (1) epithelial changes, (2) cyst formation, (3) fibrous hyperplasia and (4) lymphocytic infiltration. These features exist in varying combinations and proportions and some may be entirely absent. The cysts, which vary from microscopic size to several centimeters in diameter, are believed to be dilated ducts rather than glands. They are lined by a single layer of flattened or cuboidal epithelium. Obstruction of ducts by epithelial debris and retarded involution have been offered as explanations of the cyst formation.

Hyperplastic epithelial changes are usually present in ducts and glands. Solid buds of epithelial cells may be formed, or localized proliferations of the lining of ducts cause irregular papillary projections into the lumen. Bridges of epithelial cells may unite opposite walls, or the lumen may be completely filled by the proliferative epithelium. Sometimes the hyperplastic epithelial cells are large, clear, or pale, of a type suggesting sweat gland epithelium. Irregular atrophic changes may be present in the epithelium instead of hyperplasia. In those cases where intraductal proliferation is marked and papillary masses fill the lumen, a distinction from neoplasm, either duct papilloma or carcinoma, may be very difficult. Such distinction must be based on the histologic character of the cells, and the presence or absence of invasion beyond the ductal basal membrane.

Fibrous hyperplasia with increase in connective tissue stroma is usual, and occasionally the stromal overgrowth is marked enough to simulate the appearance of a fibroadenoma. Infiltration of lymphocytes in the stroma is a common but inconstant finding. Their presence originally suggested that the condition was of inflammatory nature, but they are now known to be part of the involutionary phase of cyclical activity.

Sclerosing adenosis is a term commonly applied to a lesion which is easily and frequently misinterpreted as carcinoma.¹⁴ A localized and somewhat lobular area of glandular hyperplasia undergoes fibrosis. The dominant overgrowth of hyalinizing connective tissue, by constricting the epithelial cells, produces variability in their shape and pattern. Thin isolated epithelial columns result, and microscopically

there is a simulation of invasiveness and pleomorphism. However, in this benign lesion mitoses are absent except in the florid stage and nuclear staining is regular.

Myoepithelial cell proliferations in the breast, either alone or in cases of cystic mastitis or fibroadenosis, if not recognized are easily misinterpreted as malignant, as has been pointed out by Kuzma.¹⁸

Mazoplasia.—The term mazoplasia was introduced by Cheatele and Cutler,³ referring to a diffuse nodularity of the breasts, without cyst formation, but with pain, usually related to menstrual periods. They felt this condition was more physiologic than pathologic, had no etiologic relationship to carcinoma, and should be sharply distinguished from the cases of "chronic mastitis" in which cysts or papillomas occur. The condition is common between 30 and 40 years of age.² This condition of painful mammary tissue is referred to by others¹ as "mastodynia."

The changes in mazoplasia are desquamation of epithelial cells filling and distending terminal ducts and acini, hyperplasia of connective tissue about the ducts and acini, and accumulation of lymphocytes.

Relationship to Carcinoma.—The relationship of chronic cystic mastitis to carcinoma has been a greatly debated point and obviously is of importance. That it is not precancerous and causes no great likelihood of malignant change has been the view of Bloodgood and others. At the other extreme, Cheatele and Cutler³ consider that at least 20 per cent of breast carcinomas have passed through the type of chronic cystic mastitis which they term "cystiphorous desquamative epithelial hyperplasia." Whether or not chronic cystic mastitis should be considered a truly "precancerous" lesion, statistical studies by Warren⁶ and by Weller and Logie⁸ have shown that it is associated with a definitely greater likelihood of development of breast cancer. The cancer attack rate for women with chronic mastitis in the age groups from 30 to 49 years was found to be 11.7 times the rate for the general female population. While this risk is insufficient to justify bilateral mastectomy for chronic cystic mastitis, subsequent careful watching is warranted.

Galactocoele.—Galactocoele is a cyst containing milk, resulting from a duct obstruction during lactation. It is a rare lesion.

Fat Necrosis of the Breast

The uncommon condition of fat necrosis in the breast is usually the result of trauma.¹⁹ The necrotic areas are opaque,

and grayish yellow or chalky in appearance. The microscopic appearance is characterized by areas of necrosis and multinucleated foreign body giant cells and hence may be confused with tuberculosis.

Mastitis and Abscess of the Breast

Acute infection in the breast is most commonly due to staphylococci or streptococci which gain entrance via a cracked nipple during the period of lactation. By one of the main ducts spread occurs into the breast substance where a localized abscess forms. Chronic periductal or plasma cell mastitis is an inflammation in and about larger ducts near the nipple, usually found in older women near menopausal age. It may simulate carcinoma on gross examination.²⁰

Tuberculosis of the Breast

Tuberculous mastitis, although rather rare, may give difficulty in clinical differentiation from carcinoma. Most cases are secondary to tuberculosis elsewhere in the body, spread to the breast commonly being from infected axillary or mediastinal lymph nodes, or by blood stream. Microscopic diagnosis is usually necessary. Since fat necrosis and plasma cell mastitis can produce a somewhat similar microscopic picture, demonstration of the organisms may be necessary for positive diagnosis.

Benign Tumors of the Breast

Fibroadenoma.—Fibroadenomas are compound epithelial and connective tissue tumors in which growth of fibrous tissue is associated with hyperplasia of glandular cells. There are two types: pericanalicular, in which fibrous overgrowth surrounds the glandular spaces, and intracanalicular, in which proliferated connective tissue projects into the ducts as polypoid masses. Fibroadenoma of the breast is not a precancerous lesion. Its occurrence does not increase the chances of carcinoma developing in the breast.

The fibroadenomas are firm, lobulated, encapsulated tumors, easily movable in the breast, and they usually remain quite small. Microscopically, the **pericanalicular** form shows marked proliferation of connective tissue around the acini, so that each tubule appears surrounded by a ring of fibrous tissue. The innermost portion of the fibrous sheath frequently shows a myxomatous change. In the **intracanalicular** form a more diffuse growth of the connective

tissue draws out and distorts the acini, so that polypoid masses of connective tissue covered by a layer of epithelium project into the lumen. If the pedicles of these masses are not included in the section, the duct lumina appear filled by rounded masses of connective tissue covered by a layer of epithelium.



Fig. 284.—Fibroadenoma of breast, partially intracanalicular.

Duct Papilloma.—Duct papilloma (adenocystoma, intracystic papilloma) is a papillary epithelial tumor which projects into a dilated duct, often quite close to the nipple. It occurs most commonly in the fourth or fifth decade and is often multiple. The tumor may or may not be palpable clinically, but discharge from the nipple, often bloody, is a common symptom. Grossly, the papilloma forms a soft arborescent papillary growth, projecting into a cystic space which contains a clear or hemorrhagic fluid.

Saphir and Parker¹⁰ have described three microscopic forms: fibrous, glandular, and transitional. The fibrous type consists of ramifying stalks of connective tissue covered by epithelium, projecting into the dilated duct. Fusion



Fig. 285.—Intracanalicular fibroadenoma of breast.



Fig. 286.—Intracystic papillary carcinoma of breast. (Courtesy Dr. H. C. Schmeisser.)



Fig. 287.—Intraductal papilloma of breast.

of the stalks results in pseudoglandular structures. The glandular type shows hyperplastic or adenomatous acini invaginated into a duct or cyst. The fibrous and glandular types are benign. The transitional cell type resembles in appearance a papilloma of the bladder. Although histologically benign, there is greater danger of carcinoma developing on the basis of this transitional cell type.

Malignancy in an intracystic papillary tumor is suggested by marked variation in size, shape, and staining of cells and their nuclei, frequent mitoses, and invasion. Penetration of the basement membrane and invasion of stroma are the most important indications of malignancy.

Cancer of the Breast

The breast is one of the common sites of carcinoma in women, but rare in males. It may occur at any adult age but is most common between 40 and 60 years. As in other carcinomas, the etiology is incompletely known. Certain factors, however, are believed important. These include hereditary susceptibility, irritation of retained secretion due to inadequate drainage by nursing following pregnancy, endocrine (estrogen) disturbances, trauma, and fibrocystic disease. While injection of large quantities of the ovarian hormone estrogen frequently produces mammary cancer in susceptible experimental animals, the relationship, if any, to human breast carcinoma is still not clear. The relationship of fibrocystic disease (chronic cystic mastitis) to cancer is likewise debatable (see p. 612). This lesion appears to predispose to development of breast carcinoma, but there is no certain means of determining which case will develop malignancy and which will not. Hence, careful watching rather than radical operative procedure appears the best choice. Trauma is rarely an important etiologic factor.

Classification into the various anatomic and histologic types of breast carcinoma is a useful procedure which may be one of the factors in determining prognosis. Such classifications cannot always be strict, however, as different portions of the tumor may show a different condition. Likewise, degree of differentiation of the tumor cells, in size, shape, arrangement, and staining also indicates the degree of malignancy. In prognosis, however, such anatomic considerations are only one factor, to be considered in conjunction with the size of the tumor, presence or absence of metastases, age and condition of the patient, pregnancy, lactation, etc.

It has been recently pointed out that, in general, the malignancy of breast cancer increases as its origin approaches the periphery of the breast.² Those which arise in large ducts near the nipple tend to form large movable tumors which ulcerate, fungate, and have a low degree of malignancy. In the mid-portion of the mammary duct system arise tumors of moderate malignancy, some developing on the basis of fibrocystic disease. At the periphery of the breast, in the terminal ducts and acini, are encountered the small, highly anaplastic, most malignant breast tumors.



Fig. 288.—Medullary carcinoma of breast. (Courtesy Dr. H. C. Schmeisser.)

Scirrhus Carcinoma.—Scirrhus carcinoma forms a hard nodule, most frequent in the upper and outer quadrant of the breast. The tumor is not encapsulated and soon be-

comes adherent to skin or deep fascia. The cut surface is composed of a hard, gritty, grayish, translucent tissue, with occasional opaque, yellowish areas of necrosis. There is no definite margin, but irregular lines of fibrous tissue radiate out into the surrounding tissue.

Microscopically there are thin masses and columns of epithelial cells, separated by an abundant dense fibrous stroma. Gland formation is slight; mitoses are infrequent. Scirrhus carcinoma tends to progress more slowly than the medullary type, and with less tendency to ulcerate or form a bulky tumor.

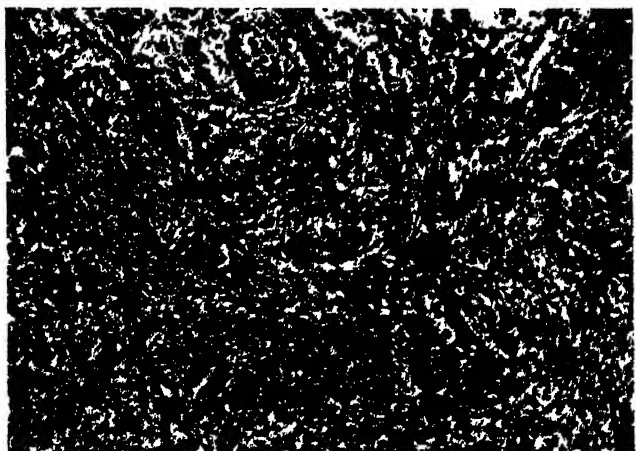


Fig. 289.—Carcinoma of breast. Strands and islands of atypical tumor cells are surrounded by a fibrous stroma.

Medullary Carcinoma.—Medullary carcinoma forms a soft, massive tumor, of relatively rapid growth, which tends to ulcerate and form a fungating mass on the surface. Microscopically, it shows masses of malignant epithelial cells, separated by a scanty stroma. There is often some tendency to gland formation.

In occasional cases signs of inflammation in the breast (edema, redness, and heat) may arise simultaneously with the development of the breast cancer, or after the tumor has been present for some time. The inflammatory signs are due to lymphatic blockage and congestion by cancer cells. The growth disseminates rapidly throughout the breast and tumor nodules appear in the skin. Such “in-

flammatory" or "acute" carcinomas progress rapidly and have a poor prognosis.

Adenocarcinoma.—Some degree of differentiation into glandular structures is not uncommon in the scirrhus and medullary forms and in the papillary tumors arising in ducts. The true adenocarcinoma, in which gland formation is predominant, is much less common. It forms a soft bulky tumor of slow growth and relatively low-grade malignancy.



Fig. 290.—Mucoid carcinoma of breast.

Duct Carcinoma.—Duct carcinoma includes two types of tumors: (1) **malignant papillary tumors** arising from ducts and often representing a malignant change in a duct papilloma; and (2) **comedo carcinoma**, so called because on the cut surface plugs of tumor cells may be expressed from ducts, giving an appearance similar to that when a comedo is expressed from a blackhead. Small dark-staining oval cells proliferate within the ducts, forming a thick lining or wall within the ducts. The tumor cells grow diffusely along ducts and for a long time remain within the ducts, so that evidence of invasion may be absent. The tumor grows slowly, metastasizes late, and has a relatively favorable prognosis.

Mucoid (Gelatinous) Carcinoma.—Gelatinous carcinoma of the breast is a rare tumor which remains small for a long period, is apt to cause protrusion and enlargement of the nipple, and have a cystic character on palpation. The mu-



PLATE XI.—Paget's disease of the nipple. Numerous Paget cells in different stages of degeneration are seen in the epithelial layer. Some plasma cells are seen in the subepithelial papillae. (From McCarthy, Lee: Histopathology of Skin Diseases, St. Louis, The C. V. Mosby Company, 1931.)

coid nature is evidenced grossly in the tumor by a gray, translucent appearance, which may be diffuse throughout or involve only a portion of the tumor. When the gelatinous change occurs in a papillary cancer or adenocarcinoma, the change is apt to be diffuse. Those showing partial mucoid change are usually of the scirrhus type. The gelatinous material is secreted by the tumor cells. Microscopically there are nests of tumor cells surrounded by loose stroma distended with mucoid material.

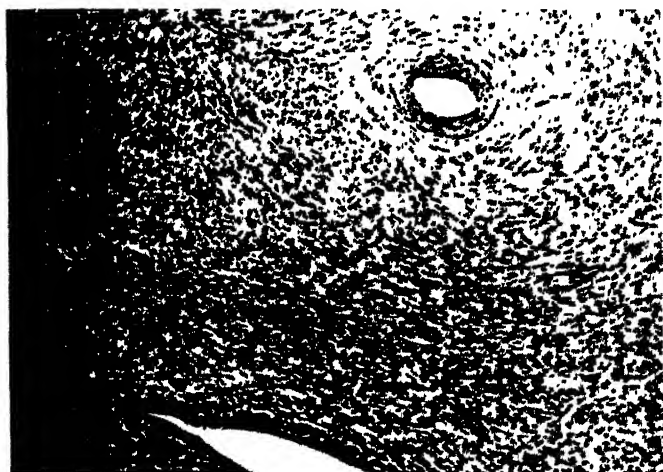


Fig. 291.—Sarcoma of breast. Remnants of epithelial structures are evident (adenocarcinoma).

Paget's Disease of the Nipple.—Paget's disease begins as a chronic eczematous lesion of the nipple, often with extension to adjacent skin of the breast, and later development of a duct carcinoma in the underlying breast. Section of the involved skin shows characteristic clear, hydropic, "Paget" cells in the epidermis. The exact relationship of the epidermal change to the underlying duct cancer is a matter of debate. Rarely, a similar change in epidermal cells is found in other parts of the body. The carcinoma associated with Paget's disease of the nipple has a relatively low degree of malignancy.

Sarcoma of the Breast.—Sarcoma is an uncommon tumor of the breast. It may arise from the connective tissue stroma, from a pre-existing fibroadenoma, from fat, or from underlying muscle tissue.

Adenosarcoma, which represents a malignant form of adenofibroma, is the most frequent type. The malignant transformation of the connective tissue is accompanied by epithelial elements. The tumor tends to remain circumscribed until a considerable size is reached, but there is a marked tendency to recurrence following local removal.

Cystosarcoma phylloides (giant mammary myxoma) is a very large bulky tumor of slow growth derived from a fibroadenoma. Grossly, it has a cauliflower-like appearance, with multiple frond-like masses, or cystic spaces into which project polypoid masses. Microscopically, myxomatous connective tissue is the predominant feature, forming polypoid masses covered by a layer of epithelium. While characteristically benign in nature, and successfully treated by wide local excision, malignant (sarcomatous) variants have been described.¹⁶

SPREAD OF CANCER OF THE BREAST

Direct invasion and metastasis by lymphatics and by blood stream are all important in breast cancer. Scirrhus carcinoma particularly tends to invade adjacent tissues, often involving pectoral muscles. Spread by lymphatics may be by direct growth along the channels (lymphatic permeation) or more commonly by tumor emboli. Lymphatic spread to axillary nodes is most common, but occasionally there is early involvement of mediastinal nodes. Spread to supraclavicular nodes is usually a late feature. Pleural and lung involvement may be by direct extension through the pectoral fascia to subpleural lymphatics, or from mediastinal nodes. The liver occasionally is invaded by a spread through lymphatics of the coronary ligament. Spread by blood stream gives rise to metastases in the red marrow of bones.

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CHAPTER XXIII

THE SKIN

The general principles of inflammations, infections, and neoplasms apply in involvement of the skin as elsewhere, modified in some instances by the position and structure of the skin.

Structure

The skin is composed of two main layers, the epidermis and corium. The epidermis, or outer portion, has a well-defined basal layer of columnar cells next to the corium, which dips down between papillae of the corium to form interpapillary processes. The cells of the basal layer undergo a gradual change to the flattened, resistant, cornified squamous cells found on the surface. In the intermediate layers of the epidermis the so-called "prickle" cells have prominent protoplasmic threads forming intercellular bridges. The outer cornified layer of epidermis may undergo excessive growth (hyperkeratosis), be imperfectly cornified (parakeratosis), undergo degeneration or abnormal cornification (dyskeratosis), or may be atrophic with diminished cornification. Tumors arising from epidermal cells are common. Inflammatory lesions involving epidermis produce vesicles and bullae (edema), pustules, and finally ulcers.

The corium is the inner layer of skin, beneath the epidermis. It is a fibrous, elastic, and fatty layer which contains hair follicles, sebaceous glands, blood vessels, lymphatics, and nerve endings. The fat cells are usually in the deepest part of the corium, often referred to as subcutaneous tissue. In inflammations of the skin it is usually in the corium that cellular, vascular, and degenerative changes are most prominent. Hypertrophy, atrophy, and neoplasia are types of pathologic change which affect elements of the corium. Sebaceous glands are small racemose glands which occur in association with hair follicles. They may undergo hypertrophic, atrophic, cystic, and neoplastic changes. The sweat glands are tubular glands which form a coil. The common type is a small gland which discharges through a spiral duct passing through the epidermis. Larger sweat glands, known as apocrine glands, open into hair follicles and are found mainly in the axillary and genital

regions. Sweat glands may be diminished in number, but functional disorders are more common than anatomic changes. Rarely, tumors may arise from sweat glands (spiradenoma, carcinoma). Blood vessels, lymphatics, and nerves of the corium, in addition to involvement in inflammatory processes, may give rise to tumors. Disturbances in the fat of the corium usually take the form of an abnormal deposit (xanthoma) or a neoplasm (lipoma, liposarcoma). Changes in the pigment deposits in the skin occur in a number of local and internal conditions (e.g., Addison's disease), and pigmented cells give rise to tumors (melanoma).

Infections and Inflammations of the Skin

Tuberculosis.—Tuberculosis of the skin, or *lupus*, occurs in a wide variety of forms, the common type being a localized form known as *lupus vulgaris*. The granulomatous inflammation is found mainly in the deeper layers of the corium. The cellular changes are similar to those of tuberculosis elsewhere, with the accumulation of epithelioid cells, multinucleated giant cells, and lymphocytes. Caseation is uncommon, however, and it is difficult to demonstrate tubercle bacilli in the tissues. The overlying epidermis may be unchanged, atrophic, or irregularly hypertrophic. Other skin lesions in which a tuberculous origin is suspected include *scrofuloderma* and *erythema induratum*.

Leprosy.—The leprosy bacillus most commonly affects skin (nodular form) and nerves (anesthetic form), although lesions may also be found in liver, spleen, lymph nodes, testicles, and elsewhere. The lesions of leprosy are similar in each situation. The histology is quite characteristic and acid-fast bacilli are usually easily demonstrable.

The skin is most commonly involved, irregular nodules or elevations affecting the face, hands, and feet, and less commonly the trunk. Sections from these nodules show an atrophy and flattening of the epidermis, and characteristic changes in the corium. In this latter situation there occurs a peculiar granulomatous reaction, characterized by swollen mononuclear cells containing abundant intracytoplasmic lipid. In ordinary sections the lipid is dissolved out, the cells exhibiting a pale, vacuolated, and foamy cytoplasm (foam cells). These cells vary in size, some of them being giant cells and occasionally multinucleated. They are phagocytes, and clusters of the causative bacilli (*globi*) are readily demonstrable in them, as well

as in endothelial cells lining blood vessels and lymphatics. The lepra bacillus multiplies within these cells. An abundant network of loose connective tissue and blood vessels is present in the lesion. A tuberculoid form also occurs, in which the histologic picture closely simulates tuberculosis.



Fig. 292.—Nodular (lepromatous) leprosy.

Lepra bacilli and the tubercle bacilli are distinguished by the following points: the lepra bacilli are numerous in the lesions, intracellular, and arranged in masses or bundles; they are straight, plump, and contain coarse granules; tu-

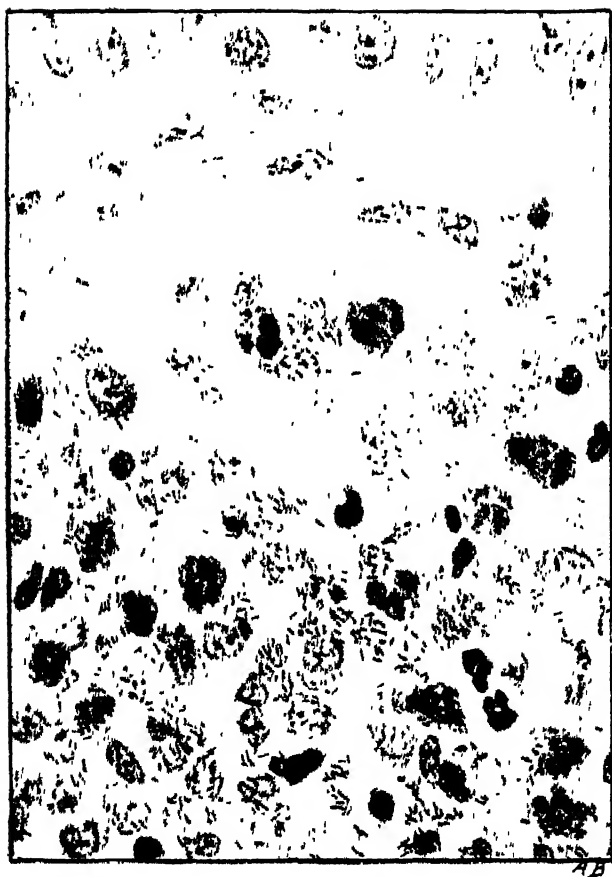


PLATE XII.—Lepra bacilli in tissues. Stained by carbolfuchsin-methylene blue, the organisms are seen extracellularly in bundles and also intracellularly as "globi." (From McCarthy, Lee: Histopathology of Skin Diseases, St. Louis, The C. V. Mosby Company, 1931.)

bercle bacilli are scarce in skin lesions, occur singly or in small groups, and are slender, bent, and finely granular.

Anesthesias of skin are due to involvement of nerves by the bacilli with development of the characteristic lesion. Trophic and traumatic lesions develop in the anesthetic areas.

Blastomycosis.—In blastomycotic infection of the skin there is irregular epidermal hypertrophy with down-growing interpapillary processes. Areas of edema develop in the epidermis, with infiltration of polymorphonuclear leucocytes and formation of tiny abscesses. The doubly contoured, round, yeast-like organisms can usually be found in these epidermal abscesses. The underlying corium is infiltrated by leucocytes, plasma cells, lymphocytes, and sometimes giant cells. The organisms may be seen in such areas of the corium as well as in epidermis (see p. 155).

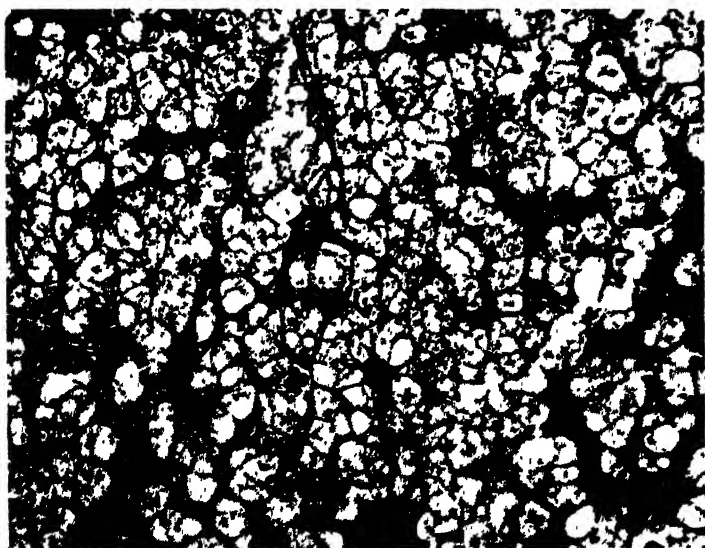


Fig. 293.—Rhinoscleroma, showing the large pale Mikulicz cells.

Rhinoscleroma.—This rare granulomatous inflammation of the nose has specific histologic features. The subepidermal tissue is packed with plasma cells, among which are characteristic large pale cells with a small nucleus and foamy cytoplasm and known as Mikulicz cells. Causative bacilli,

similar to Friedländer's bacilli, are found in the cytoplasm of the Mikulicz cells. Hyaline bodies are present in the cytoplasm of other cells. The area undergoes a gradual fibrosis.

Verruca Vulgaris.—The common wart, or verruca vulgaris, is apparently infective in origin and due to a filtrable virus. There are hypertrophy of both the outer keratinized layer and of the prickle-cell layer and irregular downward prolongations of the interpapillary process. There may be some infiltration of chronic inflammatory cells about blood vessels of the corium.

Tumors of the Skin

PRECANCEROUS LESIONS

A variety of skin and mucosal conditions, while not themselves neoplastic, give rise to carcinoma so frequently that they may be termed "precancerous." These are: (1) the keratoses—senile, solar, localized (cutaneous horn), and arsenical; (2) occupational dermatoses (tar products); (3) x-ray and radium dermatitis; (4) xeroderma pigmentosum; (5) leucoplakia; (6) kraurosis.¹

Keratoses.—The keratoses are characterized by a hyperkeratosis or thickening of the outer cornifying layers of epithelium. This may be accompanied by atrophy of remaining portions of the skin, as in the keratoses of old age and keratoses (solar) due to excessive exposure to sunlight, which are not uncommon among farmers and sailors. A localized hyperkeratosis may produce a finger-like projection or cutaneous horn. Arsenical keratosis develops usually on the palms or soles, due to continued absorption of the drug.

Occupational Dermatoses.—The occupational dermatoses are chronic inflammatory conditions or hyperkeratoses due to long-continued irritation by certain chemicals. Tar and mineral oil and their products and derivatives are most important in this respect.

Radiation Dermatitis.—Dermatitis due to overexposure to radium or x-rays is particularly apt to occur in certain sensitive skins and often has carcinoma as a late sequel. The carcinomatous change is usually preceded by hyperkeratoses, fissures, ulcers, or scars.

Xeroderma Pigmentosum.—In xeroderma pigmentosum there is abnormal sensitivity of the skin to sunlight. The condition usually appears in infancy or early childhood and

ends in death from carcinoma before adult age. Exposed areas of skin develop spotty pigmentations, warty hyperkeratoses, atrophy, and telangiectasia, and multiple carcinomas appear. The disease appears to be inherited, with an incomplete sex linkage, rather than as a simple recessive.

Leucoplakia.—Leucoplakia is a localized hyperkeratosis of mucous membrane epithelium, characterized by white thick patches. It is apparently due to a local chronic irritation. Fissures and ulcerations tend to develop and predispose to development of carcinoma.

Kraurosis.—Kraurosis is an atrophic change in the mucosa of the vulva. It is believed in some instances to be a predisposing factor in the development of squamous carcinoma (see p. 603).

More rarely, carcinoma also may develop in other skin lesions, such as the scars of burns, lupus vulgaris, lupus erythematosus, etc.

CARCINOMA OF THE SKIN

In the epidermis the two innermost layers are most active, i.e., the basal layer and the spinous-cell layer. The outer layers which undergo physiologic degeneration and death (keratinization) have little or no growth activity. Hence the main types of carcinoma of the skin arise from or simulate the inner active layers of epithelium and are known as: (1) basal-cell carcinoma and (2) squamous-cell carcinoma (spinous-cell carcinoma). There are also mixed forms, in which the fundamental types of basal and squamous cells are present in varying proportion. Finally there occasionally occurs a carcinoma arising from special structures of the skin, such as hair follicles, sebaceous or sweat glands.

Carcinoma of the skin develops usually after middle age. It occurs particularly on exposed and unprotected parts of the skin, i.e., face, neck, arms, etc. Injury by excessive exposure to sunlight, heat, wind, x-rays, arsenicals, and other chronic irritants seems to be important in causation. The development of actual cancer is often preceded by benign keratoses, or other "precancerous" lesions. Being readily accessible, treatment usually results in cure if the lesion is recognized in time. Size when first treated is important in prognosis. Lesions more than 5 centimeters in diameter have a high mortality. Most lesions less than 1 centimeter in diameter can be cured. The histologic grade of malignancy is next in importance in prognosis.

Basal-Cell Carcinoma (Rodent Ulcer).—Basal-cell carcinoma is the most frequent type of skin cancer, being particularly common on the upper two-thirds of the face, about the nose and eyelids. It is a tumor of low-grade malignancy

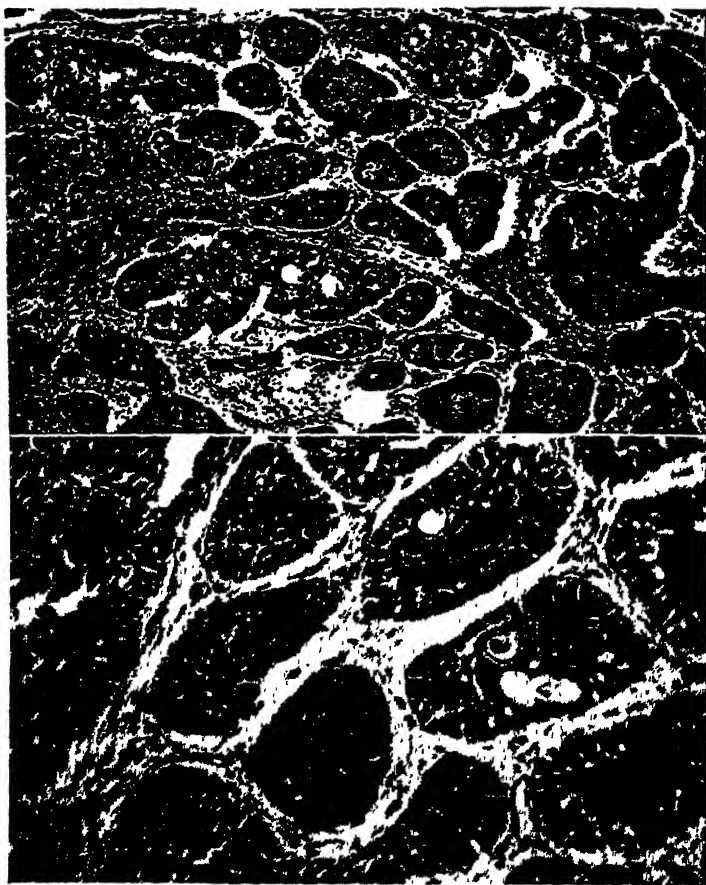


Fig. 294.—Basal-cell carcinoma of skin.

and slow growth. It rarely metastasizes but erodes its way into surrounding tissues with ulceration and much local tissue destruction. This is the “rodent ulcer” form. It may also have a nodular or fungating form.

Microscopically, the tumor is composed of cords and masses of cells with deeply basophilic nuclei. Each mass of cells tends to have a definite margin composed of a palisaded row of cells which stain deeply with hematoxylin. Mitotic figures are not abundant. There is ordinarily no keratinization, or prickle cell formation. However, in about 10 per



Fig. 295.—Squamous-cell carcinoma of finger. (Courtesy Dr. H. C. Schmeisser.)

cent there is some prickle cell formation or a few nests of keratinization. Occasionally the pegs of basal cells tend to form a glandular or adenoid picture. Excessive pigment is sometimes present, so that the tumor is easily confused with a melanoma on gross examination.

Squamous-Cell Carcinoma.—Squamous-cell carcinoma (epithelioma, acanthoma) occurs not only in the skin, but also wherever squamous or transitional epithelium is found.

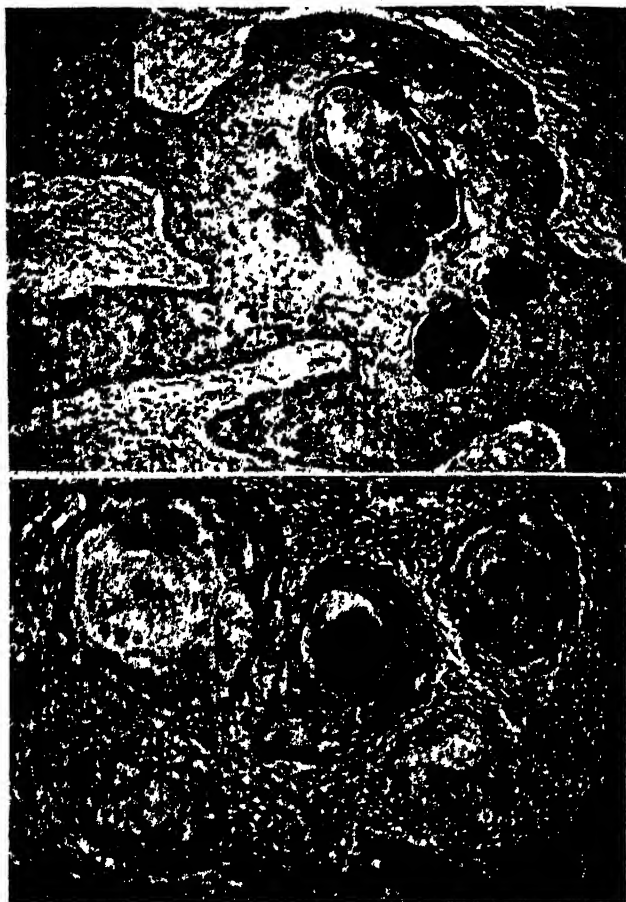


Fig. 296.—Squamous-cell carcinoma. Note the rounded masses of keratinized material.

Hence it may involve the lip, mouth, tongue, larynx, cervix uteri, bladder, and esophagus. It may also arise in other situations, e.g., bronchial mucosa or gall bladder, presumably by a metaplastic change of the lining epithelium.



PLATE XIII.—Epithelioma adenoides cysticum. Enlarged 30 times. Irregular masses and strands of epithelial cells of basal cell type. Many of the masses of tumor cells show cystic centers containing desquamated and keratinized material. (From McCarthy, Lee: Histopathology of Skin Diseases, St. Louis, The C. V. Mosby Company, 1931.)

Squamous-cell carcinoma of the skin, like other types, is commonest after the fifth decade and is frequently related to some chronic injury or irritation. The tumor may appear as a projecting nodular mass, or an ulcer. Growth is more rapid than in the basal cell type, and metastasis occurs to regional lymph nodes.

Microscopically, there is much greater irregularity than in the basal cell type. It is composed of irregular down-growths and masses of enlarged epithelial cells, which show marked variations and irregularities. Mitoses may be numerous and often are atypical. The amount of keratinization is variable. The keratinized cells are seen in concentric nests or "pearls." The masses of keratin and presence of prickle cells are the chief differential features for this type of tumor.

The squamous-cell carcinoma which arises from the lip, tongue, intraoral mucosa, glans penis, or vulva tends to grow, penetrate, and metastasize more rapidly than the squamous-cell carcinoma of the skin.

The lower lip is a particularly common site for carcinoma. These lesions are nearly all of the squamous cell type. The less frequent carcinomas of the upper lip are usually of the basal cell variety. Chronic irritation, as from excessive exposure to sunlight, pipe smoking, or bad oral hygiene, may be a predisposing factor. Leucoplakia may precede the formation of a carcinoma. The tumor may be papillary or ulcerative. Metastasis to submental and submaxillary nodes readily occurs (see p. 454).

Epidermal hyperplasia which develops in certain chronic ulcers or chronic inflammatory processes may imitate the appearance of squamous-cell carcinoma, and differentiation may be difficult. In this reactive hyperplasia the epidermal cells are usually limited by a definite basement membrane, and there is less irregularity of cells and architectural arrangement. The clinical features are often an aid in the differentiation.

Epithelioma Adenoides Cysticum (Brooke's Tumor).—Brooke's tumors are single or multiple, small, often familial, and occur mainly in early adult life. Histologically they may resemble a basal-cell carcinoma, but characteristically the epithelial strands have cystic spaces filled with hyaline or keratinized material. They are relatively benign.

Basi-Squamous (Metatypical) Carcinoma.—The mixed cell type of carcinoma of the skin contains prominent features

of both basal and squamous carcinoma. It is of greater malignancy than the pure basal cell type.

Tumors of Skin Appendages.—Origin of a tumor from one of the skin appendages is difficult to determine, since basal cells have the potential power of differentiation into any cells of the skin or its appendages. Basal-cell carcinomas have been thought by some to arise from hair shafts. Sweat gland tumors (spiradenomas or syringomas and hidradenomas) are somewhat more common than sebaceous adenomas (see Fig. 282, p. 604). Sebaceous gland carcinoma is easily confused with basal cell or squamous cell carcinomas but resembles sebaceous gland tissue in at least some portion.

Painful Tumors of the Skin.—The *tuberculum dolorosum*, or painful tumor of skin or subcutaneous tissue, is most commonly a glomus tumor or leiomyoma, but other varieties occasionally give pain. The glomus tumor is an angiomatous neoplasm arising from the glomus or normal arteriovenous communication of the skin (see p. 243).

Intra-Epidermal Carcinoma.—In this condition carcinoma proliferates in the epidermis, but spread or metastasis beyond this layer develops only occasionally or in late stages. One type, Paget's disease, most commonly involves the nipple region and is described on p. 621. Another variety is known as Bowen's disease.

Bowen's disease involves skin and certain mucous membranes. In the skin only about 3 per cent undergo eventual spread, but mucosal cases have a higher percentage of malignancy. The lesions are plaque-like or flat papules, and they may be single or multiple. Histologically, one sees dyskeratosis, great irregularity of epidermal structure, and mitoses, some of which may be atypical.

MELANOMA

Melanomas are tumors arising from melanoblasts, i.e., cells capable of producing melanin pigment. The pigment actually produced in a particular tumor may be small in amount or abundant. Benign and malignant forms occur. The extremely common benign form is called a pigmented nevus. The relatively rare malignant form is referred to as a melanocarcinoma or melanosarcoma. Melanomas occur most commonly in the skin but also are found in the mouth, rectum, and eye (see Fig. 5, p. 47).

The melanoblast is thought to be a modified basal cell of the epidermis and is capable of producing a pigmented ma-

terial from 3:4 dihydroxyphenylalanine (dopa) by means of an oxidizing ferment which it contains. Melanin probably is produced by oxidation of some substance closely allied to dopa and to adrenalin.

The nevus cells which compose a benign melanoma are believed to arise from a tactile sensory nerve ending of the skin or from melanoblastic cells of the basal layer of the epidermis.

Pigmented nevi are found in almost every individual. They occur in early years of life, grow to a certain size, and then remain stationary or become fibrotic. They are flat or raised pigmented lesions, with or without hair. Histologically, the epidermis is thinner than normal, and the basal layer is often heavily pigmented. Beneath the epidermis are nests of rounded or polygonal, pale staining "nevus cells," which contain variable amounts of melanin. The cells occur in islands, separated by connective tissue, but there is no sharp line of separation or encapsulation, and the cells may extend somewhat irregularly into subcutaneous tissue. It is usually considered advisable to excise those benign melanomas whose situation subjects them to constant irritation or trauma, e.g., those on the face or foot, as this predisposes to malignant transformation.

Malignant melanoma (melanocarcinoma, melanosarcoma) most frequently develops on the face, neck, and extremities. The incidence is greatest between 30 and 60 years, but it may occur at any age. The tumor is of relatively uncommon occurrence in the Negro race. Most cases appear to develop from a previously benign nevus.

Malignant melanoma is one of the most malignant of tumors. It invades blood vessels and lymphatics early, metastasizes widely, and is very radioresistant. The first metastases are often seen in the skin around the periphery of the tumor. Regional lymph nodes are involved early. Melanuria may occur when there are widespread metastases. The urine turns brown or black a short time after being voided.

The possibility of malignant change in a pigmented nevus should be entertained when there have been repeated irritations, noticeable increase in size or pigmentation, pain, or ulceration. In suspected malignant melanoma the entire growth should be widely excised, rather than biopsy of a portion. Histologic evidence of malignancy includes loss of architectural arrangement of the nests of nevus cells as well as the cytologic criteria used in other tumors. There is



Fig. 297.—Malignant melanoma of skin. The outer surface, cut surface, and microscopic appearance of the tumor. Abundant melanin pigment is evident. (From Surgery 9: 425, 1941.)

often an inflammatory reaction in the stroma of the tumor. Metastatic nodules may be more highly pigmented than the primary tumor.

Pigmented papillomas of the skin are benign epithelial tumors easily mistaken clinically for pigmented nevi, but containing no nevus cells and apparently with little tendency to malignant change.²⁷ Sclerosing hemangiomatous tumors may be highly pigmented by hemosiderin, and must be distinguished from melanotic tumors.



Fig. 298.—Keloids. (Courtesy Dr. H. C. Schmeisser.)

Tumorlike Conditions of the Skin

Keloid.—Keloids are fibromas developing in the corium, usually as the result of trauma but sometimes spontaneously. They occur in individuals having a constitutional factor predisposing to their development and are relatively more common in the Negro race. Various types of minor or severe traumatism initiate their growth. They are particularly common following burns, are frequently multiple, and may reach a considerable size.

Histologically, they are composed of bundles of dense, mature connective tissue. Mitoses are unusual except in early stages. Skin appendages are absent, and the over-

lying epidermis may be thinned out and its processes flattened. Distinction from hypertrophied scars may be difficult, though the latter tend to have a less dense connective tissue, and skin appendages may be present.

Kaposi's Disease.—Multiple idiopathic hemorrhagic sarcoma, or Kaposi's disease, is a rare condition of unknown origin and uncertain nature. The lesions are multiple and variable in form, but usually they are hemorrhagic and pigmented. They tend to involve the extremities, particularly the lower, in symmetrical fashion. Temporary spontaneous regressions occur, but eventually metastatic lesions may develop in lymph nodes and internal organs. It is undecided whether the condition should be classed as a chronic granulomatous inflammation or as a true tumor. The lesions involve corium and are characterized by abundant dilated blood vessels and lymphatics, proliferating fibroblasts and deposits of blood pigment. The histologic appearance may be similar to that of a spindle-cell sarcoma, though clinically the condition is much more benign.^{2, 3}

Mycosis Fungoides (granuloma fungoides).—Mycosis fungoides is considered by some to be a lymphoblastomatous disease of the skin related to leucemia or reticulo-endotheliosis, and by others to be an infective granuloma. In early stages there is an eczematoïd eruption, followed by a tumor phase, in which there may be ulceration. In the tumor stage there is a dense massive accumulation of cells in the corium, with thinning and flattening of the overlying epidermis. In the cellular tumor-like mass the cells are polymorphic, appearing as mononuclear cells, lymphoblasts, and plasma cells. Some polymorphonuclear leucocytes, eosinophiles, and giant cells may be present. There is commonly an involvement of internal organs in addition to skin, and the findings may be those of leucemic reticulo-endotheliosis.

Xanthoma.—Xanthomas are plaque-like or nodular lesions characterized by the presence of lipoids in a localized area of the corium. They are usually multiple, occur in various situations and quite commonly on the eyelids (xanthelasma). They may occur in association with diabetes or hypercholesteremia, but not necessarily so. Probably they should not be considered true neoplasms (see p. 431).

Histologically the characteristic feature is the presence in the corium of lipid-containing histiocytic "foam cells" and connective tissue proliferation. Lipoids can be demonstrated in the xanthoma cells, and crystals of lipid material may lie in the tissues. Giant cells are sometimes present.

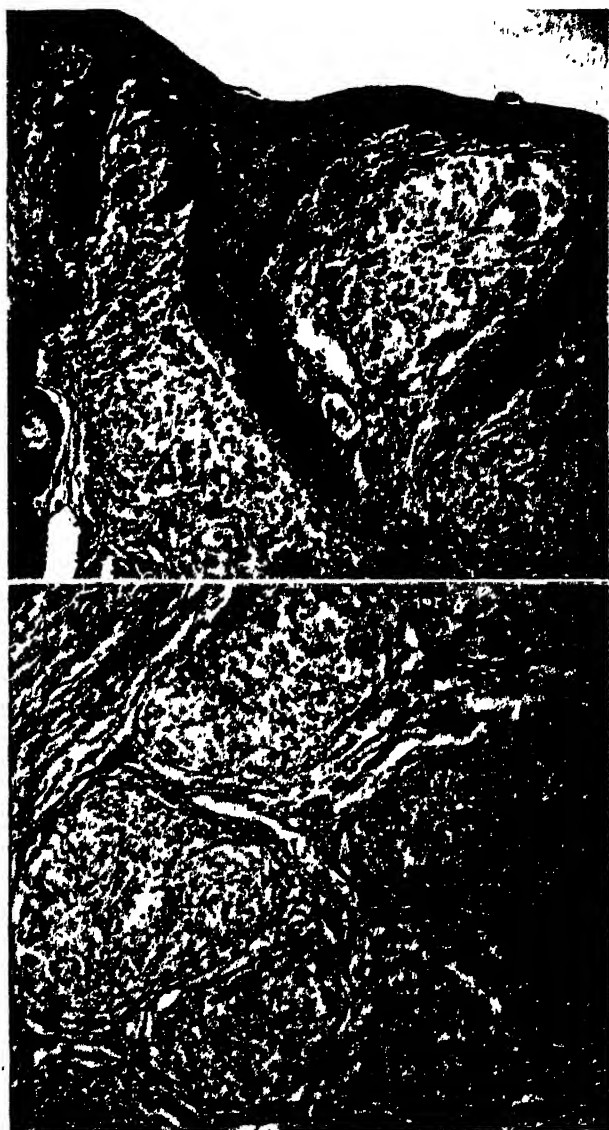


Fig. 299.—Boeck's sarcoid. Upper figure shows a lesion of the skin, and lower figure, in a lymph node. Note the rounded masses of epithelioid cells, without caseation.

Inflammatory reaction is usually evident in the diabetic xanthomas, particularly about the margins of the nodule.

Pyogenic Granuloma.—Pyogenic granuloma (Plate XIV) is an ulcerating, projecting, tumor-like mass of exuberant granulation tissue with abundant enlarged blood vessels. It appears to be the result of a chronic infection.

Sebaceous Cysts (Dermoids and Epidermoids).—The so-called sebaceous cysts, or wens, are cystic tumor-like formations in the skin, varying in size from a few millimeters to several centimeters. Within the cyst is a cheesy grayish-white substance composed of keratinized material, desquamated partially cornified cells and granular debris. The walls are composed of epidermis (epidermoid or epidermal cysts) or may have skin appendages as well, i.e., sweat glands, sebaceous glands and hair (dermoid cysts). Epidermoid cysts have a tendency to familial and hereditary occurrence, but some are of traumatic origin, due to implantation of some surface epithelium in the corium. The term "sebaceous cyst" is often loosely used in referring to almost any cyst of the skin having soft, semisolid contents. However, true retention cysts of sebaceous glands do occur, and have sebaceous gland cells as part of the lining.

Sarcoidosis (Besnier-Boeck-Schaumann Disease).—Originally described as sarcoma-like nodular lesions of the skin, sarcoidosis is now recognized as a generalized systemic disease in which there is most commonly involvement of lymph nodes, lung, bone marrow (phalanges), spleen, liver, eye, parotid, and other organs. The lesions consist of nodular accumulations of epithelioid cells, similar in appearance to the epithelioid cells in tuberculosis, with which the condition is most easily confused. Caseation usually does not occur, but when present it is not considered by some to be a criterion against the diagnosis of sarcoidosis.⁹ The clinical manifestations depend upon the organs involved. Most patients are between 20 and 40 years of age, and have a benign, but sometimes prolonged, course. Death from sarcoidosis per se is rare.

ETIOLOGY.—The etiology of sarcoidosis is unknown. It frequently has been considered an atypical form of tuberculosis, although characteristically it is impossible to demonstrate the tubercle bacillus in the lesion by staining or animal inoculation, and the patients often do not react to tuberculin injection. Harrel has suggested that it may be an exaggerated non-specific response to a lipid fraction of varied organisms. Closely related conditions in which sarcoid lesions are found include regional ileitis (see p. 488) and uveoparotid



PLATE XIV.—Pyogenic granuloma. There is an excessive growth of granulation tissue, rich in cells and containing innumerable small blood vessels and capillaries. (From McCarthy, Lee: Histopathology of Skin Diseases, St. Louis, The C. V. Mosby Company, 1931.)

fever (Heerfordt's syndrome). In this latter condition one finds low-grade chronic fever, uveitis and parotitis showing similar epithelioid lesions.

STRUCTURE.—The sarcoid lesion consists of dense nodular accumulations of the epithelioid type of large mononuclear cells. Necrosis is absent, reticulum remains relatively intact throughout the nodule, and giant cells are few. Inclusions, often of bizarre shape, sometimes are seen in the giant cells. Fibrosis develops with aging and healing of the lesions.

The points differentiating sarcoid from tuberculosis are: (1) caseation is absent or slight; (2) giant cells are relatively scarce, larger, and contain more nuclei which are evenly distributed throughout the cell; (3) a delicate reticulum is demonstrable in the lesion by silver staining, whereas in tubercles the reticulum is destroyed by caseation; (4) in the liver sarcoid lesions tend to be in portal areas, whereas in miliary tuberculosis, the midzonal region is usually involved; (5) no evidence of active tuberculosis elsewhere in the body.⁷

Biochemical changes in Boeck's sarcoid include hyperproteinemia, hyperglobulinemia, elevated serum calcium and blood phosphatase.⁸

Scleroderma.—Scleroderma may have circumscribed or diffuse thickenings of the skin, often associated with pigmentations and vascular phenomena similar to Raynaud's disease. The pathologic changes are mainly proliferation of connective tissue (fibrosis) and changes in small arterioles leading to narrowing of their lumens. These changes involve viscera, such as heart, lungs, and kidneys, as well as skin. Atrophic changes occur in voluntary muscles.

Dermatomyositis.—Dermatomyositis is an inflammatory and degenerative condition of skin, subcutaneous tissue, and striated muscles. While many features suggest an infective origin, no organism has been found and the etiology is unknown. Inflammatory changes in small blood vessels of involved tissues often appear as an important feature. The histological changes are not specific for dermatomyositis, but are similar to those of scleroderma and other conditions, and resemblances to disseminated lupus erythematoses have been noted.

The skin shows atrophy of the epidermis, edema, swelling of endothelial lining of small vessels, and perivascular and diffuse infiltration of lymphocytes and plasma cells. Muscle fibers show focal lymphocytic infiltration and degenerative changes varying from swelling and loss of striations to hyaline or vacuolar changes and necrosis. Sarcolemmal nuclei

may be increased, and giant cells are sometimes present. Creatinuria usually occurs. Vital muscles of deglutition and respiration may be affected, and promote terminal pneumonia. Heart muscle as well as skeletal muscle may be involved.

Disseminated Lupus Erythematosus

Disseminated lupus erythematosus has been recognized to be associated with important systemic and visceral manifestations involving particularly the heart and kidneys. It occurs most commonly in middle age and in women. The duration may be a few weeks to several years, but the prognosis is poor. The etiology is unknown. It is considered

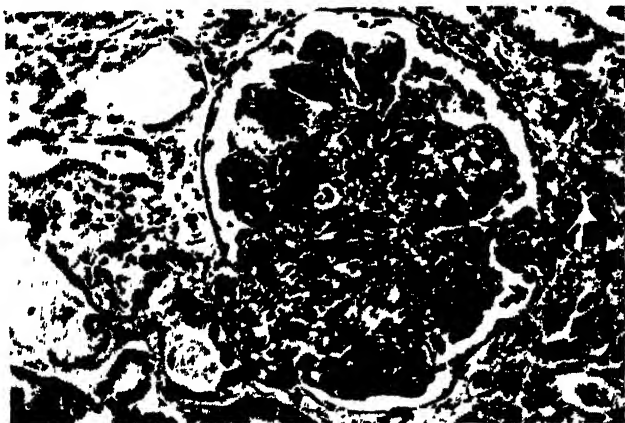


Fig. 300.—Glomerular lesion of the kidney in a case of disseminated lupus erythematosus. (U. S. Army Medical Museum, courtesy Major Arthur C. Allen.)

by some to be a chronic infection and formerly was believed to be tuberculous. Some evidence suggests that the condition may be an allergic reaction of tissues.¹³ There appears to be a disturbance of cellular metabolism, and hyperglobulinemia is constantly present. This increase in globulin is chiefly in the gamma fraction.¹² The essence of the condition has been stated to be a widespread and characteristic alteration of collagenous tissue, with a special predilection for injury to collagen of the heart, glomeruli, blood vessels, skin, spleen, and retroperitoneal tissues.¹⁰

The histologic changes in the skin lesions consist of hyperkeratosis and edema of the epidermis, and dilatation of

lymphatic and small blood vessels of the corium with perivascular lymphocytic and polymorphonuclear infiltration.¹¹

Nonbacterial atypical verrucous endocarditis, as described by Libman and Sachs, occurs in a considerable proportion of cases (see p. 259). Renal changes also are frequent but not constant. The kidneys are of normal size or enlarged. Glomerular capillaries have a characteristic "wire-loop" appearance due to hyaline thickening of the basement membrane, and capillary thrombi are frequent (Fig. 300).

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CHAPTER XXIV

BONES, JOINTS, AND TENDONS

BONES

The bones are not inert matter, but active living substance influenced by vascular and biochemical factors, endocrine and nutritional changes, infections, and trauma. The bone marrow has the important function of blood formation.

Bone formation occurs by a process of ossification and calcification. In long bones there is ossification in cartilage (endochondral ossification), i.e., there is first a growth of cartilage, which later degenerates, disappears, and is replaced by bone formed by osteoblastic activity. In flat bones of the skull, bone is formed in membrane (intramembranous ossification) by differentiation of connective tissue cells into osteoblasts which progressively lay down bone. A long bone increases in length by progressive ossification on the diaphyseal side of the growing epiphyseal cartilage. Increase in width of a bone occurs by formation of new bone on the surface under the periosteum. With increase in width, the marrow also increases in size due to resorption of adjacent bone by osteoclasts.

In formation of bone, a proper supply of calcium and phosphorus is essential. For this there must be a sufficiency of dietary mineral intake, sufficient vitamin D to promote absorption of calcium, and proper function of the parathyroid glands. The calcium is laid down in bone in the form of a complex calcium phosphate and calcium carbonate compound, with the assistance of an enzyme, phosphatase, which hydrolyzes phosphoric esters to form inorganic phosphate. Phosphatase is found in high concentration in growing bone. Vitamin C also is essential for bone formation. Skeletal growth is controlled by the anterior lobe of the hypophysis.

Once deposited in bone, the calcium is not necessarily there permanently but is in a storehouse from which it may be quickly and easily withdrawn. Mobilization of calcium from the bones is brought about by parathyroid hormone. Excess of this hormone will raise the level of calcium in the blood at the expense of the bones. The calcium and phosphate concentration of the blood is very stable and delicately balanced by storage or removal from bones. Bone absorp-

tion is brought about mainly by the action of osteoclasts (bone phagocytes). They may be multinucleated and are similar to foreign body giant cells.

The normal structure of bone is maintained by the balance of osteoblastic and osteoclastic activity. When under pathologic conditions there is excessive osteoblastic activity, osteosclerosis results. When osteoclastic activity predominates, the result is osteoporosis (atrophy) of bone. Atrophy may result from senility, pressure, hyperparathyroidism, inflammation, disuse, and dietary deficiency. In hyperparathyroidism and in old age the atrophy tends to be generalized. Local atrophy may be the result of pressure (e.g., by a tumor or aneurysm), disuse, or inflammation.

Disturbances of Circulation

Like other tissues, bone is dependent on adequate blood supply for preservation of its structure and function. Certain circulatory malformations, e.g., arteriovenous fistula, sometimes affect the circulation of a limb and cause overgrowth of the bone. Necrosis (infarction) occurs in bone when the circulation is seriously reduced. This is commonly a result of trauma, and in fracture some necrosis usually occurs near the ends of the fragments. Fracture or dislocation of the hip may interrupt the blood supply through the ligamentum teres, and result in aseptic necrosis of the head of the femur.¹ Blockage of circulation in bone in adults may cause infarction or secondary arthritis deformans.²

Osteodystrophy

The osteodystrophies are a group of conditions in which there is abnormality of development, form, or structure of bone. Some are congenital (achondroplasia), others due to endocrine disturbances (osteitis fibrosa cystica) or dietary deficiency (rickets), and others are of obscure or unknown origin.

Giantism.—The effects of endocrine factors on skeletal growth are well illustrated by the occurrence of giantism and dwarfism as a result of endocrine disturbance. Overproduction of the growth hormone of the anterior pituitary during the period of growth produces the most extreme cases of giantism (see p. 518). Acromegaly is a skeletal overgrowth due to hyperpituitarism in adult life (see p. 518).

Dwarfism.—Failure of proper development of the long bones during the growth period may be due to hypopituitarism (pituitary dwarf), hypothyroidism (cretin), and

chronic renal insufficiency (renal dwarfism). In this latter condition hyperplasia of the parathyroids is probably a factor (see p. 303). Various other abnormalities of bone development, such as oxycephaly, gargoylism, etc., are more obscure in their cause and pathogenesis.

Achondroplasia (*chondrodystrophia fetalis*) is one of the most frequent forms of dwarfism. Here there is extreme shortness of the bones of the extremities, while the bones of the trunk and head have developed to normal size. Endochondral growth and ossification have been deficient, so that the bones are short, but disproportionately thick. The condition is often evident at birth. Intelligence is not affected.

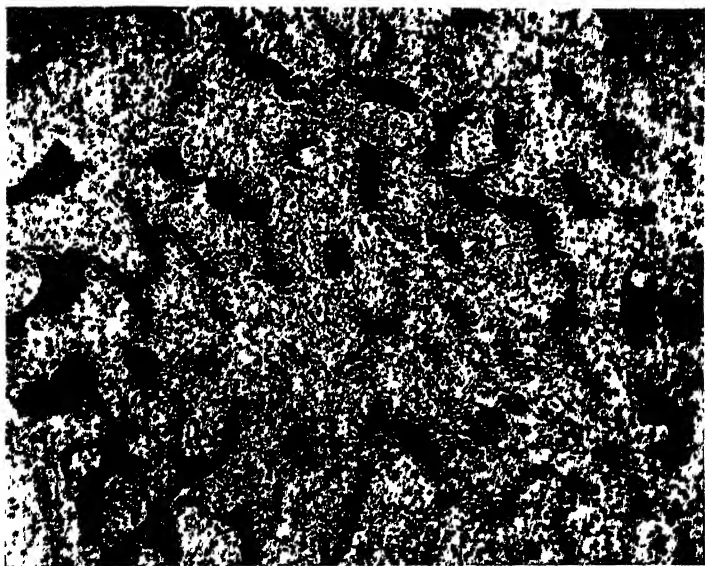


Fig. 301.—Osteogenesis imperfecta. Very delicate well-calcified bone trabeculae within fibrous tissue. Osteoblasts of irregular shape and arrangement. (Courtesy Dr. W. H. Bauer.)

Osteogenesis Imperfecta.—Osteogenesis imperfecta (*fragilitas ossium*) is a hereditary and familial disease, in which there is mesenchymal hypoplasia. Blue sclerotics are often present, the sclerotics being thinner than normal and defective in fibrous tissue so that the underlying pigmented choroid shines through. The bones have thin cortices, with a decrease in the cancellous elements. The trabeculae of the

medulla are delicate and widely separated. The delicate bones fracture with extreme ease, and affected infants are often born with multiple fractures. In other cases fractures and deformity develop later. Healing occurs with abundant callus but poor ossification. There is a characteristic disturbance of dentine, similar to that in the bones. Deafness due to otosclerosis develops in many cases.³

Osteopetrosis.—In osteopetrosis (marble bone or Albers-Schönberg disease) great increase occurs in the thickness and density of the bones and profound anemia (osteosclerotic anemia) develops due to encroachment on the hemopoietic tissue of the marrow. The ultimate etiology is unknown, but there seems to be a familial factor. The vertebrae, pelvic bones, base of the skull, proximal ends of the femurs and distal ends of the tibiae are most affected. Though of increased density, the bones are "chalky" and tend to fracture more easily than normal.⁴

Skeletal Lesions in Nutritional Deficiencies.—Skeletal lesions form a prominent feature in scurvy due to vitamin C deficiency (see p. 194), in rickets due to vitamin D deficiency (see p. 195), and in osteomalacia. Osteomalacia is the adult counterpart of rickets, due to deficient supply of calcium and vitamin D. It is rare except in countries where under-nutrition is marked, occurs almost exclusively in women, and is aggravated by the high calcium demand of pregnancy. The lumbar vertebrae, pelvis, and long bones of the lower limbs are most affected, and marked pelvic deformities may interfere with childbirth. The changes are less limited to growing ends of bones than in rickets. A large proportion of poorly calcified osteoid tissue composes the soft bones, so that they are gradually bent and deformed by muscles and tendons. The bone marrow is fibrous, gelatinous, and sometimes hemorrhagic, and as in rickets, the parathyroids are often found to be enlarged.

Fibrous Dysplasia of Bone.—Polyostotic fibrous dysplasia of bone (osteitis fibrosa disseminata) appears to be a defect of development⁵ involving mainly bone but sometimes extra-skeletal tissues as well. Symptoms of pain, disability and deformity of a limb usually begin in childhood, and the disease runs a slow and protracted course. The skeletal lesions, usually multiple, are entirely or predominantly unilateral, and most common in the femur and tibia. The lesions are roentgenologically similar to those of osteitis fibrosa, but uninvolved skeletal areas show no decalcification. Serum calcium is normal or only slightly elevated, calcium balance and

serum phosphorus are normal, and serum phosphatase is increased.⁶ In some cases there have been pigmented areas of the skin and (in females) precocious sexual maturation.

The lesions show a thinning of the cortex of the bone, and a replacement of the spongiosa and marrow by a rubbery whitish fibrous tissue, which is gritty from the presence of spicules of newly-formed bone. Cyst formation is absent although there may be small areas of focal cystic degeneration. Microscopically, fibrous tissue replaces the spongiosa and fills the marrow cavity, and is irregularly traversed by tiny trabeculae of primitive, poorly-calcified new bone. Small islands of hyaline cartilage may be present.

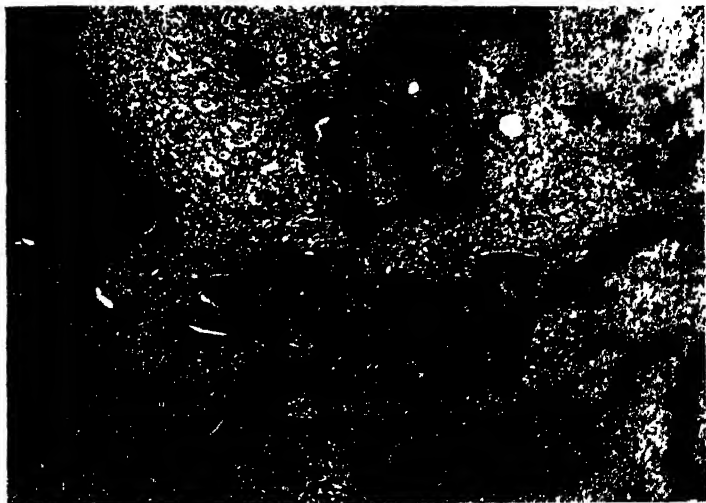


Fig. 302.—Fibrous dysplasia of bone. Newly-formed thin bone trabeculae in a loose stroma of immature stellate cells. (From a solitary lesion of the femur of a girl 8 years of age, courtesy Dr. W. H. Bauer.)

Generalized Osteitis Fibrosa Cystica.—Osteitis fibrosa cystica (von Recklinghausen's disease) is due to hypersecretion of parathyroid hormone, usually the result of an adenoma in one gland. It is characterized by distortion of the skeleton due to lack of sufficient mineralization and replacement of the osseous tissues and marrow spaces by fibrous tissue. In advanced cases there are giant-cell tumors and cysts. Associated with the disease one finds decreased



Fig. 303.—Osteomalacia and rickets. Upper: Osteomalacia (symphysis pubis). Well-calcified remnants of old bone are coated with extremely wide osteoid tissue. Lower: Rickets, note the broad osteoid zones surrounding well-calcified bone trabeculae. (Courtesy Dr. W. H. Bauer.)

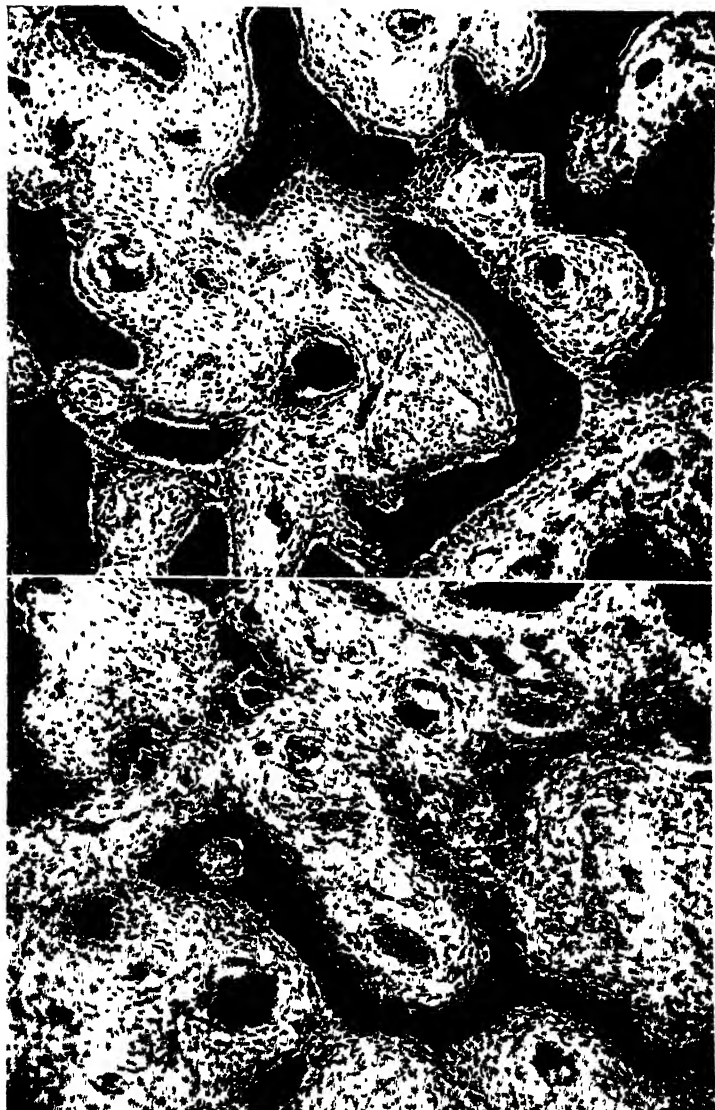


Fig. 304.—Osteitis fibrosa cystica (von Becklinghausen). Note the irregular arrangement of newly formed bone trabeculae, which exhibit narrow osteoid zones and osteoclastic resorption. The marrow is fibrous and hyperemic. (Courtesy Dr. W. H. Bauer.)

neuromuscular sensitivity to galvanic stimulation, hypercalcemia and hypophosphatemia, increased serum phosphatase, and often metastatic calcification in other tissues, particularly kidney.

The change in osteitis fibrosa is essentially an osteoclastic resorption of bone and its replacement by connective tissue in which there are abortive attempts at new bone formation. This may be of any degree. When mild, the gross change in the bones is merely a slight porousness, and microscopically, mild generalized osteoporosis and marrow fibrosis. With progression of the condition there is more and more loss of osseous tissue, and it is replaced by connective tissue. Immature poorly calcified bone develops in the connective tissue. The newly formed bone soon may again undergo resorption. Osteoclasts are abundant. Large fibrous scars develop in the place of the original spongy bone. Some of the lesions are brownish and are often called brown or giant-cell tumors. The brown tumors are areas of round and spindle cells, fibroblasts, and giant cells. The giant cells show phagocytosis of red cells or hemosiderin, which imparts the brown color to the lesion.⁷

Cysts are not always formed, and the presence of neither cysts nor brown tumors is necessary for the diagnosis. The cysts may be minute or large, single, multilocular, or multiple. They result from degeneration or hemorrhage and are lined by connective tissue.

When osteitis fibrosa is marked, the involved bones are soft, easily deformed or cut, and the skeletal lesions may be varied, with extreme decalcification, deformities, cysts, and giant-cell tumors. The long bones and spine are most markedly involved, followed by pelvis, skull, and jaw. The degree of functional stress and strain apparently is a factor in localization.

Hypertrophic Pulmonary Osteoarthropathy.—In hypertrophic pulmonary osteoarthropathy there is symmetrical enlargement ("clubbing") of the distal phalanges of the fingers and toes, with swelling of the joints. Subperiosteal deposition of bone is increased, with thickening of connective tissue around the bone and joint. These changes are usually associated with conditions of chronic anoxemia, or with some toxemia. Chronic lung abscess, bronchiectasis, empyema, pulmonary tumors, and congenital cardiac defects are conditions with which this phalangeal lesion is often associated.

Inflammatory Lesions of Bone

The skeletal tissues, like the soft tissues of the body, respond to injuries by a process of inflammation. In many cases the injurious agent is of bacterial nature, as in osteomyelitis caused by staphylococci, but other inflammatory processes are of more obscure etiology. In the acute inflammations it is the periosteum, the contents of the Haversian canals, and the bone marrow that are mainly involved. In the more chronic processes changes in the osseous portions are also prominent, as in this case there is time for changes to occur in the hard tissues.

Osteomyelitis.—Bacteria may reach bone directly through a wound, e.g., a compound fracture; may spread to bone from an adjacent tissue, e.g., from a suppurative infection of a tooth or of the middle ear; or may be brought to bone by the blood stream from a distant focus of inflammation, e.g., tonsillitis. When the inflammation is restricted to periosteum, it is properly called a periostitis; when involving bone substance, an osteitis. In most cases bone and marrow tissue are involved as well as periosteum, and the term osteomyelitis is commonly used.

Acute hematogenous osteomyelitis is mainly a disease of childhood and is rare after the age of 30 years. It is due usually to the *Staphylococcus aureus*, but in rare cases to streptococci or typhoid bacilli. The original focus of the organisms is often not discoverable, though sometimes it is an obvious furuncle or carbuncle. At the onset fever, local pain, and leucocytosis occur. Radiologic changes in the involved bone are not discernible in the early acute stage.

The affected focus is usually in a long bone of an extremity, and situated close to the end of the diaphysis near the epiphyseal cartilage, or more superficial and lying just beneath periosteum. These are situations in a growing bone which have relatively high vascularity and are subject to trauma. Spread of the infection may be outward, to form a subperiosteal abscess, and inward to reach the central canal and thence spread widely in the bone. In most cases the epiphyseal cartilage opposes spread to the epiphysis. Purulent exudate forms, which may be seen in the Haversian canals, marrow spaces, and beneath the periosteum. Fragments of bone become necrotic, influenced by thrombosis of Haversian vessels. This dead bone (sequestrum) undergoes digestion and removal only very slowly and with great difficulty. Its continued presence prolongs the inflammation and prevents healing. An irregular casing of new bone

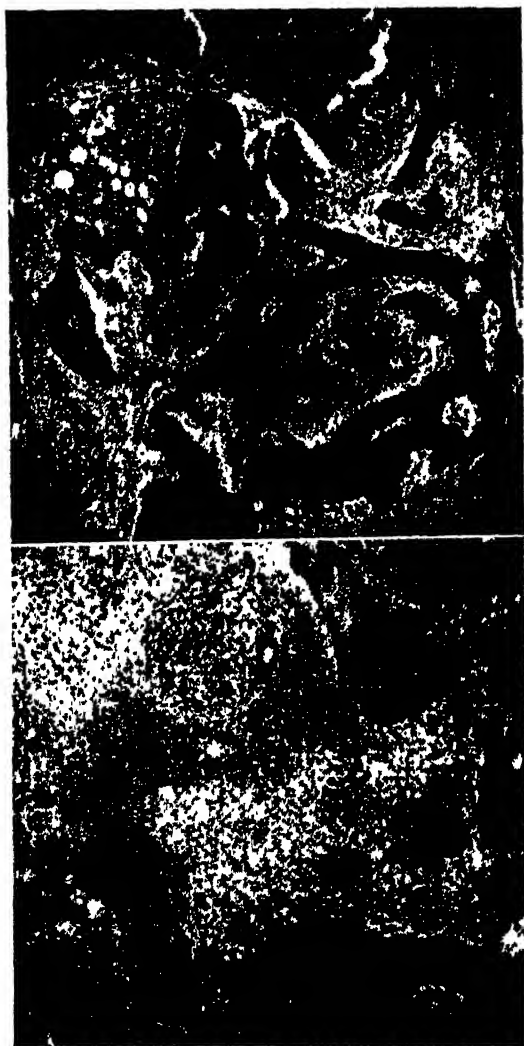


Fig. 305.—Osteomyelitis and tuberculosis of bone. Upper: Osteomyelitis of the tibia. The edematous bone marrow is infiltrated with leucocytes. Sequestrum is evident just above the center. The trabeculae of new bone are irregularly calcified. Lower: Tuberculosis of bone. Note the areas of caseation, giant cells, and lymphocytes surrounding the bone trabeculae. (Courtesy Dr. W. H. Bauer.)

(involucrum) may form around the sequestrum. Occasional complications of acute osteomyelitis include extension into a joint, formation of fistulous tracts, and pyemia. Some cases become chronic and persist for years with draining fistulous tracts. Amyloidosis may occur in such cases.

Brodie's abscess is a circumscribed focal chronic osteomyelitis. In most cases the chronic abscess is found in the upper end of the tibia. It may be the sequel of an acute osteomyelitis with organisms of low virulence.

Nonsuppurative Inflammations.—There are a number of localized conditions, apparently of inflammatory nature, but in which specific etiology is not known. **Sclerosing osteitis** (Garre's disease) is characterized by intense pain in a local area of dense cortical bone. **Osteochondritis deformans** (Legg-Perthes' disease, coxa plana) is a caries and rarefaction of the head of the femur in children 5 to 10 years of age. A similar rarefaction of bone affects the tibial tubercle in **Osgood-Schlatter's disease**, the tarsal scaphoid in **Köhler's disease**, and the semilunar bone of the wrist in **Kienböck's disease**.

Osteitis Deformans (Paget's Disease of Bone).—Paget's disease of bone is a curious condition which usually occurs after the age of 50 years. It is characterized by osteoclastic resorption of bone and simultaneous overgrowth of new, poorly calcified, irregular bony spicules. There is also excessive periosteal growth of bone with deficient calcification. The result is increase in thickness of bones with simultaneous marked softening, so that severe bowing or other deformities occur. The spine, sacrum, femur, cranium, sternum, pelvis, tibia, and jaws are most commonly involved. The blood phosphatase is high, but blood calcium and phosphorus concentrations are not changed. The calcium balance is positive, and the parathyroid glands are apparently uninvolved. Osteogenic sarcoma may be a terminal feature of some cases.

Grossly, the thickened bones are often extremely soft, light, and porous, though in late stages a more hardened state may develop. Microscopically there is evidence of osteoclastic resorption and formation of new bony trabeculae. Between the new trabeculae there is an excessive amount of loose connective tissue. Irregularly shaped plates of new and old bone stain with varying degrees of density and are separated by irregular lines of ground substance, a feature which imparts a mosaic appearance to the bony tissue. This mosaic arrangement is the diagnostic characteristic of the microscopic appearance of the bone in fully developed Paget's disease.

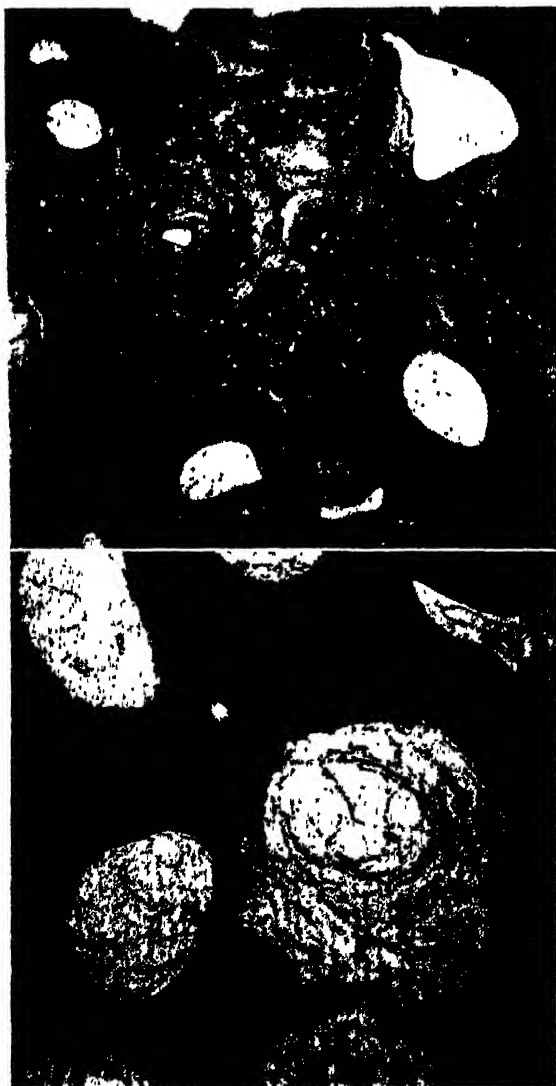


Fig. 306.—Paget's disease of bone. Upper: Note the mosaic structure. Lower: Fibrosis of the fatty marrow is proceeding from the periphery of the marrow space. (Courtesy Dr. W. H. Bauer.)

Syphilis of Bone.—Syphilis, either congenital or acquired, may produce a chronic granulomatous osteitis or periostitis. In congenital syphilis, epiphysitis affecting long bones is particularly characteristic. The epiphyseal line is irregularly widened, opaque, and a yellowish-gray color. Microscopically, there is marked irregularity of bone formation in this area, with a chronic inflammatory reaction and marked endarteritis and periarteritis. In acquired syphilis there may develop an actual gumma, or a chronic granulomatous periosteal infection of bones with spread into the subjacent bony tissue. Periarteritis and endarteritis are also prominent in the skeletal lesions.

Tuberculosis of Bone.—A chronic granulomatous form of osteomyelitis is caused by the tubercle bacillus. Children are the victims more frequently than adults. The bovine form of the organism accounts for a small proportion of cases. The infection is brought to bone by the blood stream in most cases, although the primary focus is often insignificant and may be difficult to find. The vertebrae, ends of the long bones of the legs, and bones of the hands and feet are the most frequent sites. Bony trabeculae are gradually destroyed and replaced by tuberculous granulation tissue or by caseous and creamy material. In long bones either epiphysis or diaphysis is involved, and spread often occurs to the adjacent joint.

Tuberculosis of the vertebrae (Pott's disease of the spine) usually occurs during childhood. Several vertebrae may be involved. The lesions start in the bodies, produce bony destruction, and spread similarly to destroy adjacent intervertebral discs. Thus weakened, the affected vertebrae tend to collapse, producing an acute ante flexion or angular kyphosis. Complications include compression of the spinal cord, and extension of the tuberculous pus to produce a "cold abscess," which may burrow beneath the psoas muscle and appear as a swelling in the inguinal region.

Eosinophilic Granuloma of Bone.—Eosinophilic or solitary granuloma of bone occurs mainly in children and adolescents. Although several bones may be affected, more commonly only one is involved. The lesion may be seen in almost any bone and gives rise to local pain and tenderness. Systemic manifestations are usually absent. The blood may show a leucocytosis or eosinophilia in some cases.

The involved area of bone shows a soft brownish granulation tissue, which may have yellowish streaks or regions of hemorrhage and cyst formation. Microscopically, there are

collections of phagocytic large mononuclear cells, among which are eosinophilic leucocytes and lesser numbers of multinucleated giant cells, lymphocytes and plasma cells. In late stages, the eosinophiles may be scarce, the large mononuclear cells have abundant foamy cytoplasm, and fibrosis develops. The prognosis is good, as the lesions heal following radiation or curettement, or even spontaneously.¹⁰ It has been suggested that eosinophilic granuloma is a variant of a basic process of inflammatory histiocytosis, other examples of which are Hand-Schüller-Christian disease and Letterer-Siwe disease.¹¹

Traumatic Injuries of Bone.—Minor injuries may cause a localized periostitis. In some cases this is accompanied by overgrowth of osteoid tissue (callus) in the injured area. More severe injuries may cause fracture. In children, relative elasticity of the bone may allow bending without a complete break (**greenstick fracture**). In elderly individuals bones are relatively brittle and fracture with slight trauma. In other cases very minor trauma may cause a "**spontaneous**" fracture when the bone is weakened by tumor growth or systemic disease. **Compound fractures**, in which there is communication with the exterior, are often complicated by infection. In **comminuted fractures** the bone is broken into more than two fragments.

Healing of a fracture occurs readily if the broken ends are in apposition and movement is limited. Muscle or other structures between the broken ends may prevent healing, infection retards repair, and excessive movement tends to promote fibrous and cartilagenous rather than bony union. When a bone is fractured, hemorrhage and exudation occur between and around the broken ends. This material becomes organized by granulation tissue growth. Osteoblastic activity in the periosteum and endosteum produces an overgrowth of osteoid tissue (callus) in the area. This becomes calcified and converted into bone. The excess callus in the medullary and external parts is gradually removed, and the new bone knit and shaped by osteoclasts until healing is complete.¹²

Tumors of Bone

Tumors arising in the skeletal tissues are of mesenchymal origin, and hence their malignant representatives are sarcomas. Most bone tumors tend to arise at the ends of bones near epiphyseal lines, in areas where there are complexities of growth and function. Tumors of bone are not common. Malignancies of bone probably represent about 1 per cent of

all malignant tumors.¹³ The tumors may arise (1) from external parts of periosteal tissues (periosteal fibrosarcoma), (2) from the body of the bone (osteogenic tumors), or (3) from the medulla (myeloma, Ewing's tumor). From the standpoint of malignancy and prognosis there are likewise three classes: (1) benign curable tumors, which includes exostoses, osteoma, chondroma of the phalanges, fibroma, bone cyst, and most giant-cell tumors; (2) tumors of borderline malignancy and hopeful prognosis, including central chondromas; and (3) malignant tumors, many of which are incurable, including myeloma, Ewing's tumor, etc. A modification of a commonly used classification advocated by the *American College of Surgeons* will be used here, and it is as follows:

1. Periosteal fibrosarcoma
2. Osteogenic tumors
 - A. Benign
 - a. exostosis
 - b. osteoma
 - c. chondroma
 - d. fibroma
 - B. Malignant (osteogenic sarcoma)
3. Giant-cell tumor
4. Angioma
 - A. Benign
 - B. Malignant
5. Ewing's tumor
6. Myeloma
7. Metastatic tumors
8. Inflammatory conditions simulating bone tumors
 - a. myositis ossificans
 - b. osteoperiostitis
 - c. osteitis fibrosa and bone cysts

Periosteal Fibrosarcoma.—Periosteal fibrosarcoma is a very rare tumor, most frequent in males in early adult life. It arises from the fibrous layer of the periosteum and resembles sarcoma arising from other connective tissue structures. The tumor is single, and most frequent in long bones such as the femur and ulna. It forms a fairly large, firm, whitish, circumscribed tumor, the underlying bone usually showing destructive and sometimes reactive changes. Microscopically it is similar to fibrosarcomas arising elsewhere.¹⁴

Osteogenic Tumors.—Osteogenic tumors are those which arise from mesenchymal cells having the power to differen-

tiate into and form cartilage and bone. The differentiation may be of varying degrees of completeness. In the benign forms the differentiation is advanced, so that on a histologic basis such tumors may be termed osteomas, chondromas, fibromas, osteochondromas, osteochondrofibromas, etc. In the malignant forms (osteogenic sarcoma), the formation of bone and cartilage may be very irregular or scanty.

Exostoses (osteochondromas) are benign bony or cartilaginous and bony outgrowths from the surface near the end of a long bone. They occur usually between the ages of 10 and 25 years. Microscopically, they show normal laminae of bone beneath a zone of calcifying cartilage, which in turn is thinly overlaid by fibrous tissue. **Hereditary multiple exostosis** is a developmental disturbance in which bilateral and symmetric lesions appear in juxtaepiphyseal areas. Chondrosarcomatous change sometimes occurs in one of the exostoses.¹⁵

Osteomas are rare benign tumors composed of compact bone. The term cancellous osteoma is sometimes used to refer to the exostosis or osteochondroma.

Chondroma (chondromyxoma) is a benign cartilaginous tumor occurring in the small bones of the hands and feet, ribs, sternum and spine, usually between the ages of 20 and 30. Most frequent in the phalanges of the hand, it produces a central area of rarefaction. Those arising in or about the sternum are larger tumors. Grossly, they are lobulated or trabeculated, pearly gray, and may be gelatinous or cystic. Microscopically, they are composed of fairly normal cartilage, the cartilage cells lying in pairs or tetrads in small lacunae. Certain of the cartilaginous tumors which appear to have a benign histologic structure exhibit erratic or malignant behavior and should be considered as chondrosarcomas.

Fibroma is a rare tumor of bone, usually arising from periosteum in the nasopharyngeal (see p. 459) or maxillary regions.

Osteogenic Sarcoma.—Osteogenic sarcoma is composed of osteoblastic (bone forming) cells which may be derived from the inner layer of periosteum or from the endostium. It is the most frequent malignant tumor of bone. The greatest incidence is in young people, between 10 and 30 years of age. The prognosis is better in the older patients. The common site is in the shaft of a long bone, but near the epiphysis. About 50 per cent occur around the knee. There is often a history of trauma to the area. Local pain at the site is followed by swelling. Osteogenic sarcoma is radioresistant.



Fig. 307.—Osteogenic sarcoma of humerus. (Courtesy Dr. H. C. Schmeisser.)

The tumor begins quite superficially, but extends both outward and inward, so that subperiosteal and endosteal growth occurs. In late stages the tumor produces a massive bulbous enlargement of the end of the bone. There may be a bone-destructive (osteolytic) action, or a bone-forming (sclerosing or osteoplastic) reaction induced by the tumor. In an x-ray plate of the tumor radiating spicules of newly formed bone may result in a characteristic "sun-ray" appearance. Histologically, the picture is extremely variable and complex, and skeletal tissue in all stages of differentiation and development may be found. On a histologic basis osteogenic sarcomas may be called osteosarcomas, chondrosarcomas, osteochondrosarcomas, chondrofibromyxomas, etc., depending upon the predominant types of tissue. In some cases marked vascularity, hemorrhage, and necrosis are prominent features (telangiectatic type).

Giant-Cell Tumor of Bone.—Giant-cell tumor usually involves the epiphyseal region of a long bone. It occurs in early adult life, but according to Jaffe is rare before the age of 20. Pathologic fracture may occur. Grossly, the affected skeletal area is expanded and outlined by a thin shell of bone. The tumor tissue is dark red or reddish brown in color, and of fleshy or friable consistency. Dark red areas of hemorrhage or yellowish areas of necrosis may be present. Hemorrhage and necrosis sometimes lead to a cystic change. The x-ray picture is characteristic, the tumor producing a rarified, multilocular cystic or bubble-like appearance. Microscopically, the tumor consists of spindle-shaped or ovoid cells, highly vascularized, and resembling young connective tissue. Varying numbers of multinucleated giant cells are interspersed. The many nuclei of the giant cells tend to accumulate in the center of the cell.

There are varying theories of origin of these tumors.¹⁶⁻¹⁸ It is believed by some that the giant cells represent osteoclasts, and hence the tumor has been called an "osteoclastoma." Others have suggested that it is a tissue reaction to trauma and hemorrhage that may later acquire neoplastic character. Jaffe¹⁶ considers it to be a neoplasm arising from undifferentiated supporting connective tissue of the marrow. Histologically similar tumors are the giant-cell epulis (see p. 455), the giant-cell tumor of tendon sheaths (see p. 673), and giant-cell tumors that occur in osteitis fibrosa cystica (hyperparathyroidism).

Most of the giant-cell tumors of bone are perfectly benign. The rare malignant examples are characterized by abundant

compact stromal cells with marked anaplasia, pleomorphism, and a tendency to a whorled arrangement.¹⁹

Angioma.—Angioma is an extremely rare type of tumor of bone which may be benign or malignant (angiosarcoma). It is similar to angiomatous tumors elsewhere.

Ewing's Tumor (Endothelial Myeloma).—Ewing's tumor occurs in childhood or adolescence, and involves the shaft of a long bone. It is accompanied by severe pain, fever, and leucocytosis, and hence is easily mistaken for acute osteomyelitis. Its growth in the shaft stimulates reactive formation of multiple new laminae of bone, presenting a layered onion-like appearance in an x-ray picture. The tumor is markedly radiosensitive, a characteristic often of diagnostic help, but cure by radiation therapy alone is rare.

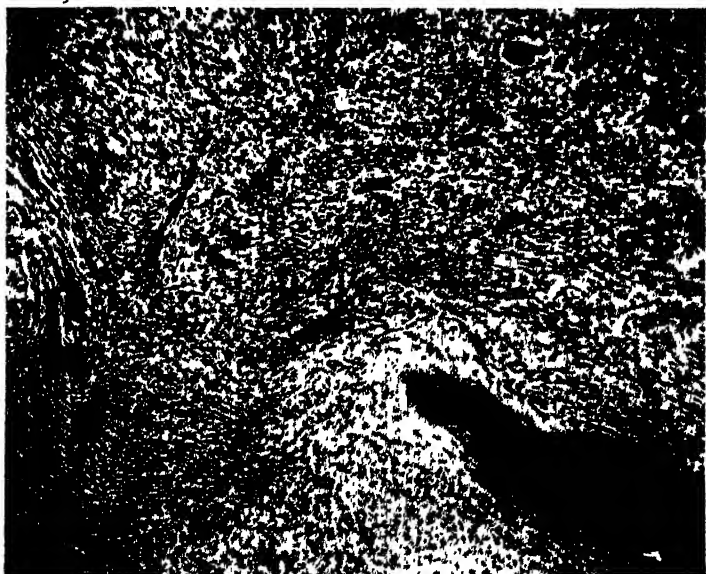


Fig. 308.—Giant-cell tumor. Note the connective tissue, numerous giant cells, and newly deposited bone. (Courtesy Dr. W. H. Bauer.)

The soft grayish tumor starts in the medulla but rapidly invades and expands the bone. The tibia, femur, humerus, fibula, and clavicle are the most frequent sites. Often more than one bone is involved. Microscopically, it is composed of small, round uniform cells, of lymphoblastic appearance, arranged in solid sheets and columns, or around blood ves-

sels. The lack of stroma is conspicuous. By silver stains, reticulin can be demonstrated surrounding groups of cells.

The origin of this tumor was originally believed to be from vascular endothelium (i.e., an endothelial myeloma), and for this there has been supporting evidence.²⁰ It also has

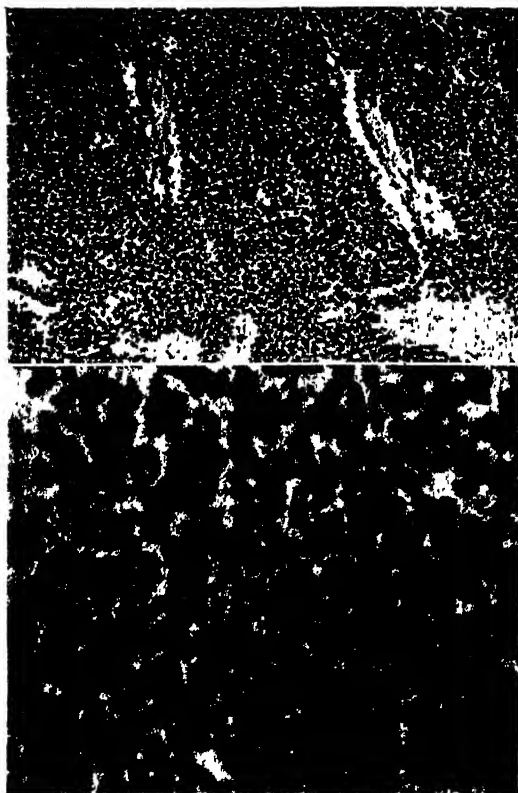


Fig. 309.—Ewing's tumor of bone.

been considered to be derived from young reticular cells, although primary reticulum-cell sarcoma of bone is said to be distinguishable by reticulin running between individual cells.²¹

Multiple Myeloma.—Myeloma is a rare, highly malignant tumor of bone marrow which either arises simultaneously in multiple sites or spreads rapidly to involve more than one

bone. Unlike Ewing's tumor and even osteogenic sarcoma, myeloma occurs in later life, at an average age of more than 50 years. The skull, spine, ribs, pelvis, femur and humerus are most frequently involved. About one-half the cases show

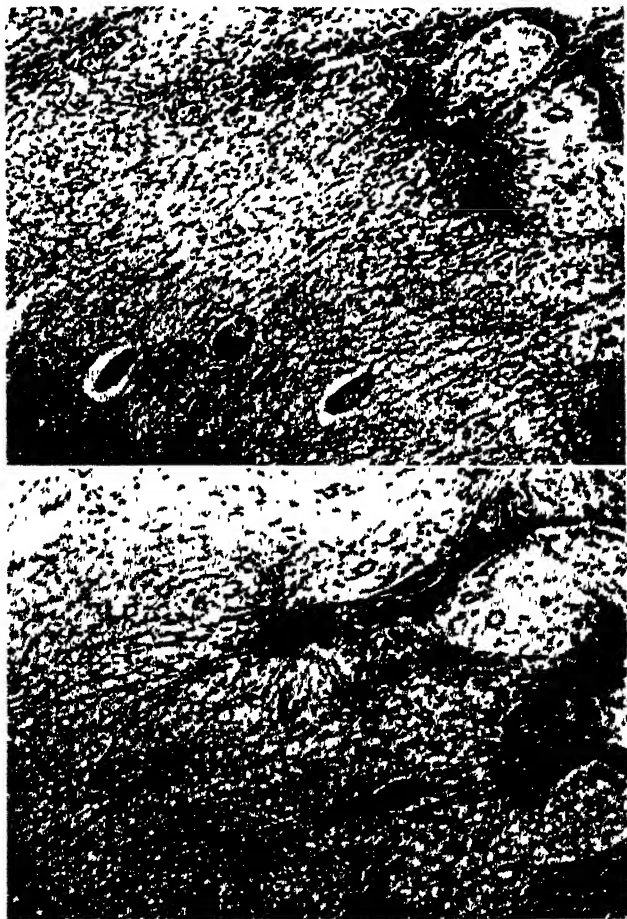


Fig. 310.—Myositis ossificans.

Bence-Jones protein in the urine. Anemia is usually present. Pain and pathologic fractures are common.

Myelomas are grayish red, soft tumors, surrounded by a thin shell of softened bone. Microscopically, they are com-

posed of densely packed sheets and masses of small round cells having the characteristic appearance of plasma cells (plasmacytoma). In rare cases the myeloma is composed of myeloblastic cells. There is little or no intercellular substance. In some cases the myelomatous tissue invades the liver, spleen, and kidneys. Multiple myeloma is invariably fatal.^{23, 24}

Metastatic Tumors of Bone.—Certain tumors metastasize to skeletal tissues with particular frequency. These include hypernephroma of the kidney, and carcinomas of the prostate, lung, ovary, breast, testis, and thyroid. Spread is by the blood stream, and the spine, pelvis, femur, skull, ribs, and humerus are the most frequent sites. The secondary tumors are often multiple, and pathologic fractures are not uncommon. The metastases are osteolytic or bone-destroying, except in the case of carcinoma of the prostate, which stimulates an osteoplastic or bone-forming reaction.^{25, 26}

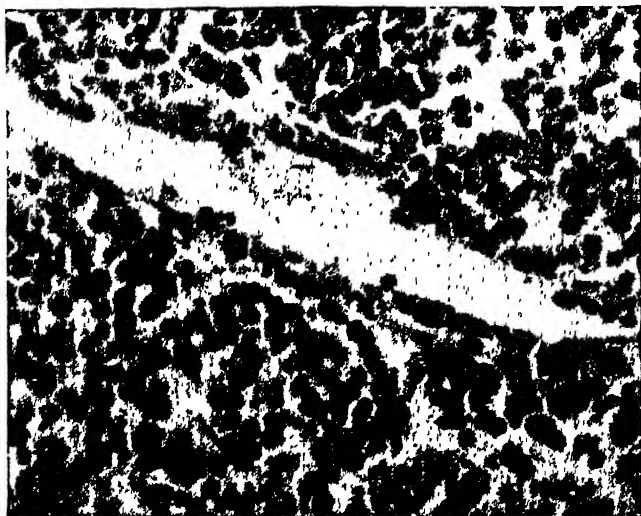


Fig. 311.—Plasma-cell myeloma of bone. (From Berman, J. K.: Synopsis of the Principles of Surgery, The C. V. Mosby Co.)

Inflammatory Conditions Simulating Tumor.—Some of the difficulties in differentiation of Ewing's tumor and osteomyelitis have been pointed out. *Myositis ossificans* is a condition in which bone develops in muscle tissue. It usually follows trauma and hemorrhage and occurs most frequently

in the quadriceps or in muscle about the elbow. The ossification may be extensive and simulate osteogenic sarcoma, and in rare cases there is actual development of malignancy. **Osteoperiostitis** is a benign condition in which areas of ossification develop in granulation tissue or hemorrhage beneath a raised periosteum. It is usually of traumatic or syphilitic origin. **Osteitis fibrosa**, in which a form of giant-cell tumor is common, is considered on p. 649.

Phosphatase

Phosphatase is an enzyme capable of hydrolyzing monophosphoric esters. It is present in highest concentration in renal tissue (see Fig. 111, p. 279), intestinal mucosa, and growing bone. In the latter site it is important in the process of ossification. Phosphatases which exhibit maximum activity in alkaline and in acid media exist and, respectively, are called alkaline and acid phosphatase. Serum acid phosphatase often is increased in patients with carcinoma of the prostate. The level of alkaline phosphatase in the serum is fairly constant for age periods. It is increased

TABLE XVIII

CALCIUM, PHOSPHORUS, AND PHOSPHATASE OF THE BLOOD IN SKELETAL DISEASES

DISEASE	CALCIUM	PHOS- PHORUS	PHOSPHATASE
Osteitis deformans (Paget's disease)	normal	normal	very high
Osteitis fibrosa cystica (hyperparathyroidism)	high	low	high
Rickets	low	variable	high
Osteoma	normal	normal	normal
Chondroma	normal	normal	normal
Chondrosarcoma	normal	normal	normal
Osteolytic osteogenic sarcoma	high	normal	normal or slight increase
Osteoplastic osteogenic sarcoma	high	normal	increased
Ewing's tumor	normal	normal	normal
Myeloma	normal or high	normal or high	normal
Metastatic tumors of bone (except prostatic)	normal	normal	normal or slight increase
Metastatic carcinoma of prostate in bone	normal	normal	high (both acid and alkaline phosphatase)

in skeletal diseases associated with marked osteoblastic activity, and in certain other conditions (e.g., jaundice). Normal values of serum phosphatase are 1.5 to 5 units (Bodansky) for adults and 5 to 13 units (Bodansky) in growing children.²⁷⁻²⁹ Table XVIII indicates the changes in serum alkaline phosphatase in various skeletal lesions.

JOINTS

Movable joints have a capsule around cartilage-covered ends of bones and are lined by a synovial membrane which encloses a cavity containing a small amount of lubricating fluid. The joint is formed of connective tissue derivatives. It functions as an organ of support and passive motion and is affected by mechanical, circulatory, neurologic, and inflammatory changes.³⁰ Diseases of joints will be considered according to the classification adopted by the American Rheumatism Association in 1941: (1) specific infectious arthritis; (2) arthritis of rheumatic fever; (3) rheumatoid arthritis (including Still's disease and Marie-Strumpell spondylitis); (4) osteoarthritis; (5) arthritis of traumatic origin; (6) arthritis of gout; (7) tumors of joints; (8) miscellaneous forms, e.g., arthritis associated with other diseases.

The numerically most important diseases of joints are rheumatoid arthritis and osteoarthritis. Being of very common occurrence, they account for a tremendous total of pain, crippling, and disability. Rheumatoid arthritis is essentially an inflammation of synovial membrane, probably of infectious origin. Osteoarthritis is a degenerative change affecting primarily articular cartilage with secondary hypertrophic changes in the underlying bone. It is often a senescent change, and possibly related to wear and tear and to changes in vascular supply.

Specific Infectious Arthritis

Infection of a joint by known organisms is usually the result of hematogenous spread in pyemia or septicemia. Less commonly the bacteria may reach the joint from an adjacent infection of bone, such as osteomyelitis or tuberculosis of bone. Also there may be introduction from without by penetrating wounds. The common pyogenic organisms which thus infect joints are the staphylococcus, streptococcus, pneumococcus, and gonococcus. Metastatic infection of joints may occur in puerperal sepsis, bacterial endocarditis, meningitis, otitis media, pneumonia, and typhoid fever.

The joint becomes swollen and acutely inflamed. Fluid accumulates in the joint cavity, at first serous but later purulent. The synovial membrane is greatly congested, swollen, and infiltrated with inflammatory cells. There may be considerable destruction of tissue, so that in healing there is formation of fibrous adhesions (fibrous ankylosis). In some cases this may be transformed into bone and a disabling bone ankylosis result.

Gonorrheal arthritis is a complication which usually develops fairly early in an acute gonorrheal infection. Several joints may be affected, but major involvement is usually in one only.

Tuberculous arthritis is commonly an extension from a tuberculous involvement of bone. It occurs mainly in children and most frequently affects the hip. The synovial membrane is greatly thickened by tuberculous granulation tissue. The inflammation may spread to erode the articular surface. Separation of flakes of cartilage or synovial fringes with adherent fibrin may form small, rounded, firm, loose bodies in the joint (melon seed bodies). Arrest may occur at any stage, or there may be rupture and sinus formation, or an end result of fibrous or bony ankylosis.

Arthritis of Rheumatic Fever

Acute nonsuppurative arthritis is often a prominent feature of rheumatic fever, particularly in the acute cases arising in adolescence or early adult life. Several joints tend to be affected in succession. Acute tenderness and swelling occur, with an excess of turbid fluid in the cavity. The inflammation is predominantly in the synovial membrane, but nodules may develop in subsynovial and periarticular tissues. The histologic character of these is similar to the Aschoff bodies of the myocardium or rheumatic nodules elsewhere. The inflammation usually subsides completely and without residual disability.

Rheumatoid Arthritis

Rheumatoid arthritis is also referred to as atrophic, proliferative, or chronic nonspecific infectious arthritis. It is a very common, chronic and disabling disease, which has its greatest incidence among women of the reproductive age. Although of unknown etiology, evidence suggests that it is a chronic infection, probably of streptococcal origin. It

usually starts gradually, but it may begin acutely and is often accompanied by general symptoms, fever, leucocytosis, anemia, etc. The small joints of the hands and feet are most frequently involved, and larger joints later. The affected joints show a spindle-shaped swelling, are very painful, and progress to deformity and limitation of movement. Subcutaneous nodules are present in some cases and show a histologic picture somewhat similar to that of rheumatic fever nodules.



Fig. 312.—Osteoarthritis. Polished exostosis extending through the articular cartilage as a result of vascularization of the cartilage from the subchondral bone marrow. (Courtesy Dr. W. H. Bauer.)

The first and essential change is in the synovial membrane, which is thickened by a granulation tissue pannus and infiltrated by many leucocytes, lymphocytes, and plasma cells. The thickened synovial membrane may develop numerous villous processes, in which there may be necrosis, hemorrhage, or fibrosis. Adjacent surfaces form adhesions, so that fibrous ankylosis tends to occur and later may become bony. The joint cartilage is attacked, with extension of granulation tissue from the synovial membrane. Inflammatory

edema and cellular infiltration are also found in periarticular tissues. An increased effusion of cloudy and highly cellular fluid is often present in the joint cavity.³²

Still's disease is an acute form affecting children. It is accompanied by fever, leucocytosis, enlargement of spleen and lymph nodes. **Felty's syndrome** is a somewhat similar condition in adults, in which chronic arthritis is associated with leucopenia and enlargement of lymph nodes and spleen. In **Marie-Strumpell spondylitis** the arthritic changes mainly involve the spine, affecting particularly the intervertebral and costovertebral ligaments. Stiffness and ankylosis of the spine result from ossification of the ligaments and fusion of adjacent vertebrae. Marked kyphosis may be present. Most cases occur in males.

Osteoarthritis

Osteoarthritis (degenerative, hypertrophic, or senile arthritis) is essentially a degenerative condition of joint cartilage with reactive and hypertrophic changes in underlying bone, rather than a primary inflammation. Affecting the sexes equally, it is a disease of later life, being common after the age of 40. Large joints, including the hip, tend to be affected, and there is little local inflammation or pain. While there may be considerable deformity and limitation of movement, complete crippling of a joint is unusual. Trauma and changes due to excessive function are most prominent in the causation of osteoarthritis, as has been discussed by Bauer.³³ Other types of injury to the joint, inflammations, synovitis, and endocrine disturbances, also may be etiologic factors.

Changes begin in the articular cartilage. The cartilage cells degenerate, and the normally smooth surface becomes ridged, frayed, and fibrillated. The elasticity of the cartilage and its cushioning function become reduced. The subchondral bone is thus exposed to excessive functional stresses and its marrow reacts to this chronic irritation by proliferative changes. Osteoclasts resorb the subchondral bone trabeculae and blood vessels penetrate into the cartilage. The vascularization of the cartilage is followed by ossification, the bone so formed becoming highly polished (eburnated). Exostoses formed in this fashion at the margins of the joint and periosteal bone formation produce the characteristic bony "lipping" at the edges of the joint. This process occurs prominently in the fingers, forming painless Heberden's nodes. Osteoarthritic changes in the spinal

column (spondylitis deformans) may produce kyphosis, extreme rigidity of the back ("pokerback"), and pain due to pressure of osteophytic growths on nerve roots. While bony ankylosis may occur in this type of spondylitis, ankylosis is an uncommon result of osteoarthritis elsewhere.

Traumatic Injury of Joints

Trauma to a joint may be followed by effusion of fluid into the joint cavity, and acute inflammation of surrounding soft tissues.

Charcot joint is a condition which occurs in certain cases of tabes and syringomyelia. Destruction of nerve fibers results in loss of sensation in the joint, which is then subjected to unusual trauma. The painless joint is excessively mobile, and destructive changes occur in the joint cartilage and adjacent bone.

Arthritis of Gout

Gout is a disease of unknown etiology, but connected in some fashion with a disturbance of purine (protein) metabolism. The uric acid content of the blood is increased, but this alone does not precipitate an acute attack. It occurs chiefly in middle-aged men and appears to be influenced by excessive indulgence in meat and alcohol.

Acute attacks commence suddenly with pain, swelling, and tenderness in a joint (toes, fingers, or knee). There is an effusion into the joint cavity of fluid containing crystals of sodium biurate. These crystals also become deposited in surrounding soft tissues where they elicit some foreign body reaction and chronic inflammation. A "tophus" is a chalky deposit of the crystals in the subcutaneous tissue, or in cartilages of the eyelid or ear.

Tumors of Joints

Only rarely do tumors arise from joint structures, but chondromas, lipomas, synoviomias, spindle-cell sarcomas, and chondrosarcomas have been described.

Synovioma.—Synovioma (synovial sarcoma) is a malignant tumor arising from the lining cells of the synovial membrane of a joint or bursa. Histologically, it shows a distorted picture suggestive of synovia, but the appearance in various examples is far from uniform. There is a groundwork of rounded or spindle cells, with epithelioid gland-like

spaces or pavement-like areas of tissue suggesting low epithelium. Mucus may be present in the gland-like spaces. Papillary villus-like structures are sometimes formed. Recurrence often follows local removal of the tumor, and pulmonary metastasis may occur. Amputation is usually necessary for cure.^{34, 35}

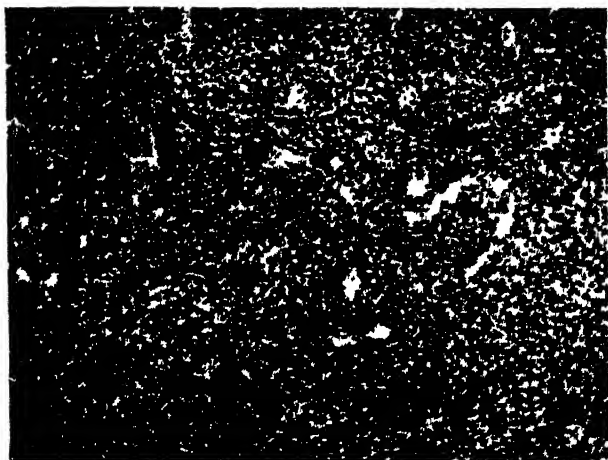


Fig. 313.—Synovioma. Note the gland-like and channel-like spaces.

TENDONS

Inflammation.—Tenosynovitis is an inflammation of tendon sheaths at the wrist or ankle. It may be traumatic, suppurative, or tuberculous. In the latter, with fibrin in the exudate, there may be formed ovoid “melon seed bodies.”

Ganglion.—Ganglion is a cyst-like swelling arising from a tendon sheath or joint capsule. It is most common on the back of the hand or wrist. There is proliferation of fibrous tissue of the sheath, with mucoid degeneration, producing the cyst-like swelling. There is no true lining, and the ganglion does not communicate with the cavity of the tendon sheath.

Tendon Sheath Tumors.—Giant-cell tumor (xanthoma) of a tendon sheath is a yellow or yellowish-brown tumor which arises near a tendinous insertion, most often in the hand. It has a groundwork of fibrous tissue in which there are scattered giant cells and aggregates of large, lipid-containing

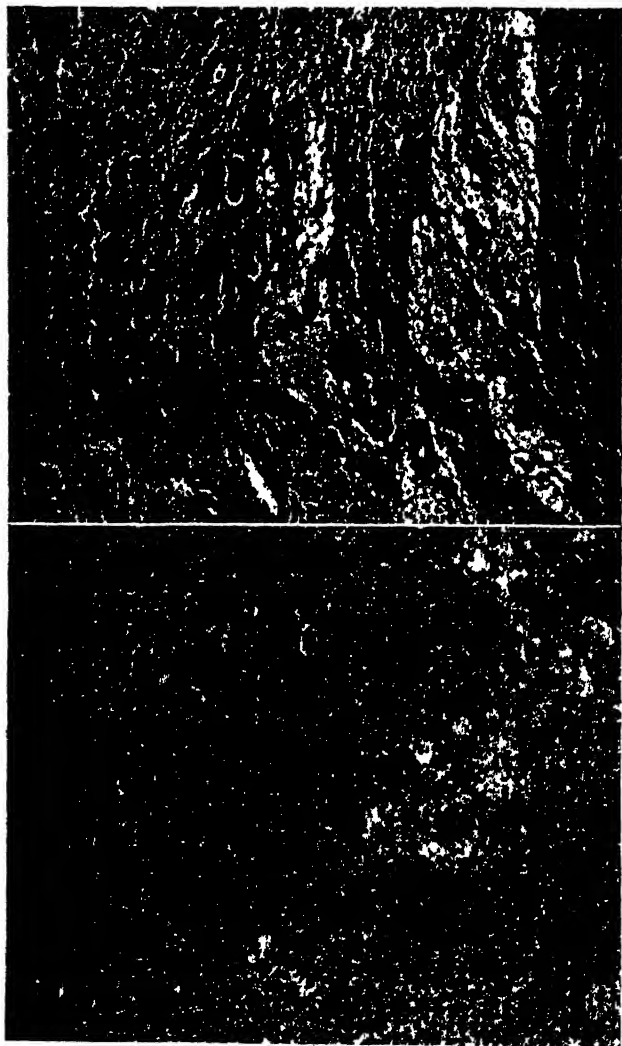


Fig. 314.—Xanthomatous giant-cell tumor of tendon sheath. Note the xanthoma cells, with distended foamy cytoplasm.

foam cells (xanthoma cells). The xanthoma cells are found when there are deposits of iron and cholesterol.³⁶ Except for this xanthomatous tendency, the tumor is similar to the giant-cell epulis and the benign giant-cell tumor of bone.

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CHAPTER XXV

THE NERVOUS SYSTEM

Structure and Reaction to Injury

The nervous system and its supporting structures include ten fundamental tissues, each of which exhibits several common types of response to injury. Some of these reactive changes appear to be specific, e.g., the rounding up of microglia to produce fat-granule cells when myelin is destroyed. Many, however, are nonspecific, and the microscopic changes are interpreted with greater difficulty.

1. Notochordal Tissue.—Remnants of this tissue are most common in the following locations: (a) along the clivus; (b) in the hypophyseal fossa, (c) deep to the posterior wall of the pharynx, (d) in the dens, (e) in the nuclei pulposi of the intervertebral discs, and (f) in the sacrum. Pathologically, notochordal tissue is encountered as a tumor (see page 688) and in herniation or displacement of intervertebral discs. Posterior protrusion of an intervertebral disc may compress the spinal cord or nerve roots, causing symptoms of root pain. The nucleus pulposus may herniate following trauma or degeneration of disc tissue. It usually occurs in later life and most commonly involves the lumbar region. Notochordal tissue (nucleus pulposus) is identifiable microscopically by its larger vacuolated mucus-containing cells set in a thin fibrillar stroma of elastic and collagenous tissue.

2. Ependyma.—The ependymal lining cells of the ventricular system of the brain and the central canal of the spinal cord retain an epithelial character. Very often they are flattened and in some regions may appear in folds or tufts, particularly in the third ventricle. During the developmental period, the ependymal cells are ciliated. Processes extend intramedullarily from the lining layer to form a thin fibrillar network immediately beneath the ependyma. The more common reactions associated with ependymal tissue include proliferation, subependymal gliosis, and inflammation. **Proliferation**, manifested by reduplication to several layers of cells, may appear as an aging process. This is common in lower levels of the spinal cord, sometimes to such an extent that the central canal appears obliterated. **Subependymal gliosis** appears to be a response to a chronic toxemia or anoxia as in alcoholism, the subependymal layer becoming greatly thickened and densely sclerotic. **Inflammation (ependymitis)** is

seen in septic conditions of the ventricles and as a result of irritation of the lining cells by other agents, such as *toxoplasma*. The subependymal layer is swollen and infiltrated with neutrophilic leucocytes, and the lining cells are reduplicated, festooned and swollen, or may be eroded.

3. Neuroglia.—The intramedullary supporting glial cells are astrocytes and oligodendroglia. In sections stained by hematoxylin and eosin they must be differentiated by nuclear configuration. The nucleus of the astrocyte is large, oval, pale, and vesicular, with chromatin material deposited in small dustlike particles on a fine linin net. The nuclei of the oligodendroglia are about one-third smaller, more rounded, and stain darkly, with clumped chromatin masses. Special stains show that the astrocytes possess sucker-foot attachments to blood vessels and a great many fibrillar processes. The oligodendroglia have but few processes. Astrocytes appear in greater number in gray matter than in white. Oligodendroglia are equally numerous in both gray and white matter forming the "satellite cells" of the neurones and the "interfascicular supporting cells" of the nerve fibers.

Astrocytes may undergo either regressive or reactive changes. Regressive changes are most commonly seen as degenerative processes in tumor cells, or in severe toxemia, and are manifested by shrinkage and gemistocytosis. **Shrinkage** is identified by pyknosis of the nucleus with fragmentation and extrusion. In **gemistocyte formation** the cells swell and the cytoplasm becomes stainable by routine methods. The distal parts of the cell processes fragment and disappear while the roots become faintly visible. The nuclei are eccentric and may be multiple. These cells are often referred to as "fat-astrocytes." Reactive changes in astrocytes are represented by **proliferation**, an increase in the number by mitotic divisions; by **gliosis**, a production of glial fibrils forming a dense fibrous network and entering into repair phenomena; and by **swelling**, the visible cytoplasm increasing and varying up to the formation of "giant" astrocytes.

Oligodendroglia present three common reactive changes. **Acute swelling** and vacuolation is a nonspecific alteration which may occur as an agonal phenomenon. **Proliferation**, or an increase in number, is seen in toxic or inflammatory conditions. **Satellitosis** is an increase in the number of oligodendroglia neighboring a nerve cell body, and is seen in certain toxic states. It has been referred to as incidental to neuronophagia (see page 680). It may, however, represent an independent toxic response.

There are a number of alterations in the nervous system in which the parent reacting element is obscure, but in which glial cells may take part. **Glial nodes** are nests of proliferated glial cells, and are particularly prominent in rickettsial encephalitides. As they are often aggregated close to vessels and house intracellular organisms, the cells may be derived from perithelial cells of vascular adventitia. **Glial plaques** (Alzheimer) are sclerotic nodules representing focal repair efforts. They may contain glial fibers and cells with an admixture of fragmented nerve fibers. **Corpora amylacea** are concentric hyaline bodies of disputed origin. They are common after 40 years of age and often are conspicuous in premature senility. They stain with iodine but contain neither amyloid nor fat. They resemble corpora amylacea of the prostate or the lung.

4. Choroid Plexus.—The choroid plexus may be regarded as a pia-ependymal membrane invaginated by subarachnoidal vasculature. The ependymal epithelium with a thin fibrous substrate is disposed in foliated or villous pattern with a highly vascular core composed of loose trabecular tissue resembling arachnoid. Alterations in the choroid plexus are common but usually are unimportant. Most often encountered are **cyst formation**, the thin-walled, translucent cysts appearing most frequently at the confluent part of the lateral ventricles; **concretions** (brain sand), amorphous firm bodies sometimes quite numerous; and **sclerosis**, a fibrosis of the choroid core.

5. Neuron.—The neurons are the functional units of the nervous system and by their interrelationships provide the physical basis for nervous activity. Each consists of a cell body and its processes. Microscopically, the best criterion for identification is the nucleus. It is large, round, vesicular, and contains a large nucleolus. The nuclear membrane is distinct. The cytoplasm contains varying amounts and patterns of basophilic material known as Nissl substance. Special stains enable identification of neurofibrils which traverse the cell body and continue into the processes. The shape of the cell body varies greatly; it may be multi- or unipolar and the size ranges from a diameter of a few microns to over 100, depending on location and function. From the cell bodies arise a varying number of processes, some of which (dendrites) serve to fix the cell body and provide receptive surfaces for synaptic contact. The axone is the process over which a nervous impulse is conveyed to an adjacent neuron or to an end organ. Those axones (axis cylinders) attaining

a diameter greater than 1.5 microns¹ possess a fatty covering, the myelin sheath. In the central nervous system this sheath is limited externally by the network of fibrillar processes of supporting cells (oligodendroglia). In peripheral nerves the myelin is encased in a wrapping supplied by sheath cells (Schwann). Each sheath cell has distinctly marked linear limits which form a constriction (node of Ranvier) around the axis cylinder, at which point the myelin layer is obliterated. The axis cylinders terminate in buttonlike knobs (boutons) which provide the contact points at the synapse,² or in special peripheral structures in muscle or gland.

Changes in the body of nerve cells are difficult to interpret because of the complex nature of the neuron and the distances over which the processes spread. The common reactions of the cell body are shrinkage, swelling, vacuolation, pigment changes, chromatolysis, and neuronophagia. **Shrinkage** is indicated by marked irregularity in the shape of the cell, pyknosis of the nucleus, clumping and condensation of Nissl substance, and sclerosis or contortion of processes. Shrunken cells are common in senility and other cerebral atrophies, and also may appear in chronic infections. **Swelling** of nerve cells clouds the irregular surface contour. The cytoplasm stains faintly, the processes fragment, and the cell may be evident in outline only. This change, apparently reversible, occurs in acute toxic states and mild infections. It is the most prominent change in tetanus. **Vacuolation** of nerve cells occurs in toxic states. The appearance of light brown or yellow pigment in a perinuclear position or in cytoplasmic blotches is observed commonly and is referred to as **pigment degeneration**. This degenerative process should not be confused with the normal pigment in cells of certain locations (locus caeruleus and substantia nigra). In **chromatolysis** the Nissl substance becomes fine, dispersed, peripheralized, or loses its staining properties altogether. The nucleus of the involved cell is eccentric in position. Because this change is believed to be a specific retrograde response to axone injury, it has been widely used to identify the nuclear or ganglionic origin of damaged fiber bundles in the central and peripheral nervous systems. **Neuronophagia** involves reaction of macrophages as well as nerve cells. Phagocytosis of nerve cells is common only in inflammatory diseases and is conspicuous only when the death of the cell is brought about by an intracellular agent. It is a characteristic occurrence in poliomyelitis.

A mass of macrophages may be seen occupying the position of, or within, a nerve cell body. In satellitosis, on the other hand, the cells are seen around but not within the nerve cell body. The phagocytic cells may be mononuclears from the blood, microglia, or oligodendroglia.

The reactions of the axis cylinder to injury include changes in the neuraxis, alterations at the synapse or end organs, and neuroma formation. By coating the argyrophilic neurofibrillar structure with reduced silver salts, the morphology of the axis cylinder and its terminal boutons is seen to vary under pathologic influence. The neuraxis may swell in irregular nodules or fragment and become granular. The synaptic change may be a loss of structure, or accentuation by beading and reduplication of terminal bulbs.³ The diffuse encephalomyelitides induce the most profound synaptic changes. In peripheral nerves the end organs undergo dissolution following severe damage to the nerve.⁴ Neuroma formation occurs as a regrowth reaction to traumatic interruption of nerve fibers. The neuroma is a tangle of regrowing neurofibrils, each spearheaded by a bulbous expansion, the growth cone. Neuromas may develop along the trunk of a nerve at a point of trauma or at the extremity of an amputated stump. The microscopic appearance is complicated by growth of fibrous tissue or by sheath cell proliferation. In a traumatic neuroma of some duration, these supporting elements remain and the argyrophilic substance of the neuraxes disappears.

Myelin Degeneration.—The loss of myelin substance (demyelination) is a prominent pathologic change in both central and peripheral nervous systems. In considering demyelination as an index of injury it is essential to remember that most fibers normally possess no myelin. This fatty substance, a complex of at least four lipoids, is deposited around fibers of both central and peripheral neuraxes. Injury to the cell body or axis cylinder causes a degeneration of the myelin, or its dissolution may appear spontaneously without apparent nerve injury. Demonstration of the demyelination depends principally upon the use of three staining procedures. The Weigert technique stains normal myelin blue or black. Demyelinated areas do not stain and hence are identifiable by contrast. This procedure is applicable to normal tissue and to old degenerations. The Marchi technique stains the altered lipoids of degenerating myelin directly, so that this procedure demonstrates active degeneration. Osmic acid will blacken

normal myelin. Used principally in peripheral nerve study, the failure to take osmic acid implies loss or absence of myelin.

The demyelinating process and accompanying changes occurring secondary to trauma or interruption of peripheral nerves is called **Wallerian degeneration**. This proceeds in both distal and proximal directions from the point of injury. Proximally, the observable alterations in the myelin are usually arrested at the next node of Ranvier. The node probably plays no role in this since the same limitation of retrograde change is seen in the central nervous system. Proliferation of neurofibrils proximal to the injury occurs within a few hours. Distally, the axis cylinders become granular and fragment, and the myelin undergoes dissolution and forms fat

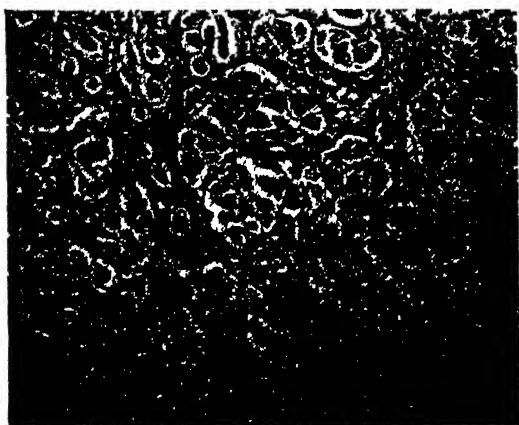


Fig. 315.—Amputation “neuroma.”

droplets. The products of degeneration are removed, mainly by macrophages, in a few weeks. Simultaneously, regenerative changes occur. The sheath cells (neurilemma, Schwann) proliferate, enlarge, and migrate from both proximal and distal stumps into the defect, bridging it and providing cytoplasmic channels for the regrowing neurofibrils from the proximal stump. The endoneural connective tissue persists, reinforcing the neurilemmal cells. Regrowth may be inhibited by scar tissue and by poor apposition of the stumps. Regrowing neurofibrils will progress at the rate of $\frac{1}{4}$ mm. per day through the scar and 3 to 4 mm. per day through the peripheral stump.⁵ Certain of the regrown fibrils slowly enlarge within the Schwann cells and accumulate a myelin

sheath. The original status of an individual myelinated peripheral nerve fiber is reestablished in nine to twelve months. The complete restitution of all fibers of a peripheral nerve probably does not occur.^{6, 7, 8}

In the central nervous system there is a somewhat different process of demyelination. The sheath cells are replaced by oligodendroglia which lack the remarkable regenerative properties of the former. Central nerve cell processes may be as inherently capable of regrowth as peripheral cells, but only those which possess a neurilemmal sheath are able to be restored. Consequently, functional repair of interrupted central neuraxes does not occur, although abortive neurofibrillar attempts at regrowth are constantly observed.^{9, 10, 11} Hence, disruption of nerve tissue with accompanying demyelination in the central nervous system is an irreversible reaction. In the area of injury or softening where a large amount of myelin is broken down, the degenerative fatty products are removed by macrophages (microglia). The degeneration of myelin progresses distally from the point of injury. The myelin appears in droplet form and acquires staining reactions which imply chemical alteration. The droplets will, however, remain in position for months, or even years, and mark the degenerating tract. Proximally (toward the cell body) the process may progress for a short distance but ordinarily is insignificant.

A second type of demyelination occurs in the central nervous system without apparent cause. (See demyelinating diseases, page 702.)

6. Sheath and Capsule Cells.—A membranous covering for peripheral nerve cell bodies and neuraxes is provided by capsule and sheath cells. Microscopically, their nuclei appear as rounded forms satellite to ganglion cells and as elongate structures along peripheral nerves. The sheath cells form a cylindrical tube threaded by a neuraxis and separated from it by a concentric sheath of myelin. When myelin is absent the neuraxis is covered intimately by the thin-walled sheath cell. Applied to the outside of the Schwann sheath are the collagenous elements of the endoneurium. The reactions to which sheath and capsule cells are subject are, principally, hypertrophy and proliferation, and these occur prominently in repair of peripheral nerves.

7. Meninges.—The coverings of the central nervous system include the dura (pachymeninx) and the pia-arachnoid (leptomeninx). The dura is adherent to the cranial periosteum (external layer of dura) but is separated widely from

the periosteum of the vertebral canal. The pia follows the surface of the brain closely and is separated from the arachnoid, which is in apposition with the dura, by the subarachnoid space. This space contains cerebrospinal fluid and is bridged by a spongy network of filaments, the arachnoid trabeculae. The principal histologic element of all membranes is collagenous tissue. Elastic fibers appear in the pia-arachnoid and in the innermost layer of the dura. Flattened mesothelial cells (meningeothelium) line the subarachnoid and subdural spaces and cover the arachnoid trabeculae. In addition to the lining cells, fibroblasts and fixed histiocytes are identifiable in the membranes. Nests of epithelial-like cells are occasionally encountered buried in the dura. These are arachnoidal rests. The common reactions of the meninges to injury include production of macrophages, and false dura formation. The macrophages are derived from meningeothelium or fixed histiocytes, or both, and appear in great number in inflammatory conditions. False dura formation amounts to a rapid repair process in which a coagulum forms, later to be invaded by fibroblastic cells. This occurs when dural continuity is interrupted and in walling off hemorrhage.

8. Vasculature and Related Structures.—Intimal, medial, and adventitial changes in cerebral vessels are similar to those occurring elsewhere. There are, however, three peculiarities in cerebral vasculature which play prominent roles in reactive phenomena. (1) Vessels less than 70 microns in diameter contain little or no muscle in the media after 40 years of age.¹² (2) In passing through the subarachnoid space the vessels acquire a meningeothelial sheath and, in penetrating to an intramedullary position, carry a second outer sheath derived from the pia lining. These concentric wrappings establish a perivascular space (of Virchow-Robin) which is continuous with perineuronal and interstitial spaces in the central nervous system. This space is the morphological basis for the reaction of perivascular infiltration or cuffing. Drainage from the interstitial spaces of the medullary substance passes through the Virchow-Robin channels and in so doing may load the space with inflammatory cells or products of degeneration. In addition, exudate reaches the perivascular space through the vessel wall. (3) Vascular adventitial elements provide the parent tissue which reacts to form an abscess wall in response to invasion by certain bacteria.¹³

9. Microglia (Mesoglia).—Microglial cells are believed to be mesodermal elements derived from perivascular tissues and are distributed widely throughout the nervous system

in postnatal life. Normally, they appear to be at rest (fixed) in which form only the nucleus is evident in ordinary sections. Compared to the neuroglia, the microglial nucleus is small, very compact, and may be irregular in shape (round, elongate, or curved). The scanty cytoplasm and thin branching processes require special staining to be demonstrated. These cells respond to the products of myelin degeneration. In this *fat-granule cell* reaction the cell processes are pulled in and

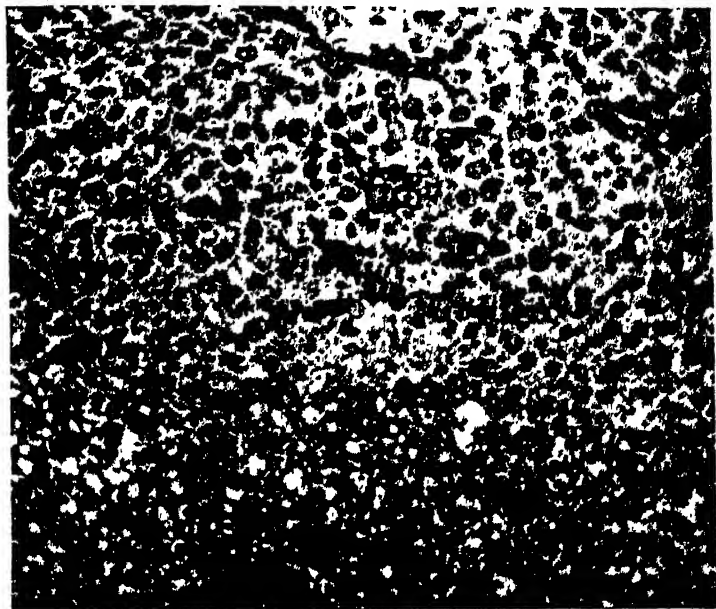


Fig. 316.—Infarct of brain. The edge is shown, and many compound granular corpuscles (microglia) are evident.

the nucleus elongates, becoming bipolar. This *rod cell* migrates to the site of injury, where the nucleus becomes rounded and lighter staining. As fat products are engulfed the cytoplasm becomes globular and the nucleus eccentric. These fat-laden macrophages (fat-granule cells, compound granular corpuscles) often migrate into the perivascular spaces. They are the characteristic cells in an area of cerebral softening.

10. The Cerebrospinal Fluid.—The cerebrospinal fluid forms a circulatory system peculiar to nervous tissue, per-

haps taking the place of the absent lymphatics. The fluid is formed from blood by the choroid plexus of the cerebral ventricles, probably by a process of dialysis, though there may be an active secretory mechanism as well. Formed mainly in the lateral ventricles, the fluid passes through the interventricular foramina (of Monro) into the third ventricle and through the narrow cerebral aqueduct (of Sylvius) to the fourth ventricle. From the roof and lateral extensions of this ventricle it escapes through the lateral apertures (of Luschka) and the median aperture (of Magendie) to reach the subarachnoid space. From the large subarachnoid cisterns at the base of the brain, it passes downward into the subarachnoid space of the spinal cord and upward through the narrow aperture of the tentorium cerebelli to bathe the surface of the brain. Most of the fluid is resorbed into the venous blood stream around the region of the vertex by way of the arachnoidal villi which project into the lumens of the venous sinuses. Some diffusion of fluid probably occurs through the perivascular or Virchow-Robin spaces by means of which interstitial fluid of the brain tissue is added to the cerebrospinal fluid.

The cerebrospinal fluid reflects by its changes many important disease processes. Normally, the volume is about 125 cubic centimeters. It is clear, colorless, has a specific gravity of 1.006 to 1.009 and contains fewer than 12 cells (mononuclears) per cubic millimeter after 12 years of age. In infants there may be 20-30 cells per cubic millimeter. In disease, there may be color changes due to fresh hemorrhage, or xanthochromia, a yellowish tinge derived from hemoglobin and implying stasis following hemorrhage. The cell content may be altered in both number and character, and chemical and serologic changes occur which are valuable aids in diagnosis. The most striking change involving cerebrospinal fluid is the mechanical effect resulting from obstruction to its flow (hydrocephalus).

Histogenesis of Nervous Tissues

The primordial tissues giving rise to the structures of the nervous system include: (1) notochordal tissue, (2) medullo-epithelium, (3) neural crest tissue, (4) neuroskeletal inter-tissue, and (5) general body mesoderm.

Tumors of the Nervous System and Related Tissues

Intracranial tumors as a group have certain peculiarities due to their position and the nature of the cells from which

they arise. Occurring within a rigid bony box, their increase of bulk causes damage in increasing intracranial pressure. This is contributed to, also, by edema of nervous tissue around the growth, and often by obstruction to the pathway of cerebrospinal fluid, with some degree of hydrocephalus. A relatively small tumor may press upon or involve vital areas of the nervous system. Most of the intracranial tumors arise from supporting structures, i.e., neuroglia, sheaths of the brain (meninges) or cranial nerves, and blood vessels. Their greatest incidence is in middle age, but certain types occur mainly in childhood. Most of them do not metastasize, but they may be locally malignant and invasive. Others are quite benign biologically but are serious because of their position.

CLASSIFICATION

- I. Chordoma
- II. Primary intramedullary neurogenic tumors
 - A. Gliomas (supporting cell tumors)
 - 1. Ependymoma
 - 2. Oligodendroglioma
 - 3. Astrocytoma
 - 4. Medulloblastoma
 - 5. Medulloepithelioma
 - 6. Pinealoma
 - 7. Glioblastoma multiforme
 - 8. Syringomyelia
 - B. Nerve Cell Tumors
 - 1. Neurocytoma
 - 2. Neuroblastoma
 - 3. Retinoblastoma
- III. Primary extramedullary neurogenic tumors
 - A. Supporting cell tumors
 - 1. Neurofibroma
 - B. Nerve cell tumors
 - 1. Ganglioneuroma
- IV. Tumors of vascular and perivascular structures
 - A. Angioma
 - B. Sarcoma
 - C. Lymphoblastoma
- V. Meningiomas
- VI. Mixed tumors
- VII. Hypophyseal tumors
- VIII. Metastatic tumors

I. Chordoma.—Chordomas are rare, slowly growing tumors derived from notochordal rests, most commonly in the sacrum and along the clivus. Grossly, the mass is gelatinous or mucinous and tends to compress or invade bone. Microscopically, they are composed of large polyhedral cells disposed in lobules or cords surrounded by a myxomatous matrix. Both cytoplasm and nucleus may contain mucus. Because of inaccessibility, complete removal is difficult and recurrence is usual.

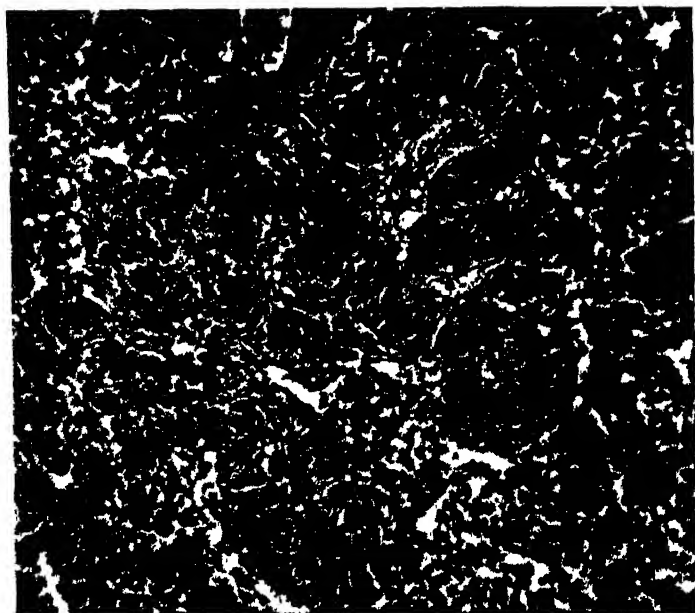


Fig. 317.—Ependymoma.

II. Intramedullary Tumors.—Tumors of nervous tissue proper include the gliomas and neurocytomas. Gliomas constitute more than half of all intracranial tumors and represent neoplasia of supporting tissues and their stem cells, whereas tumors of nerve cells are relatively rare.

Gliomas.—1. **EPENDYMOMA.**—Ependymomas comprise about 6 per cent of the gliomas. They are derived from ventricular lining cells and appear commonly in the fourth ventricle, along the central canal, and in the flum terminale. Although slow growing, they often interfere with cerebrospinal fluid

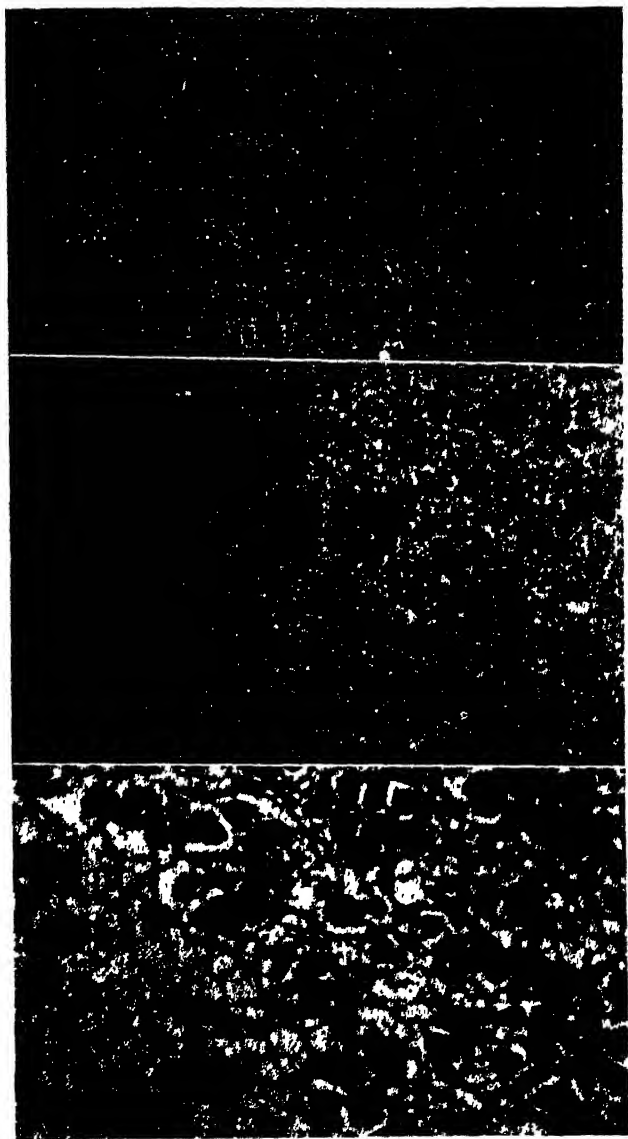


Fig. 318.—Oligodendroglioma. Note the clear halo around the nuclei of the tumor cells.

flow, producing acute increase of intracranial pressure. Grossly, they are usually distinctly demarcated from brain tissue. The histology is complex and Kernohan and Kernohan¹⁴ have grouped them as: (a) papilloma choroideum, a papillary tumor of the choroid plexus, closely simulating the

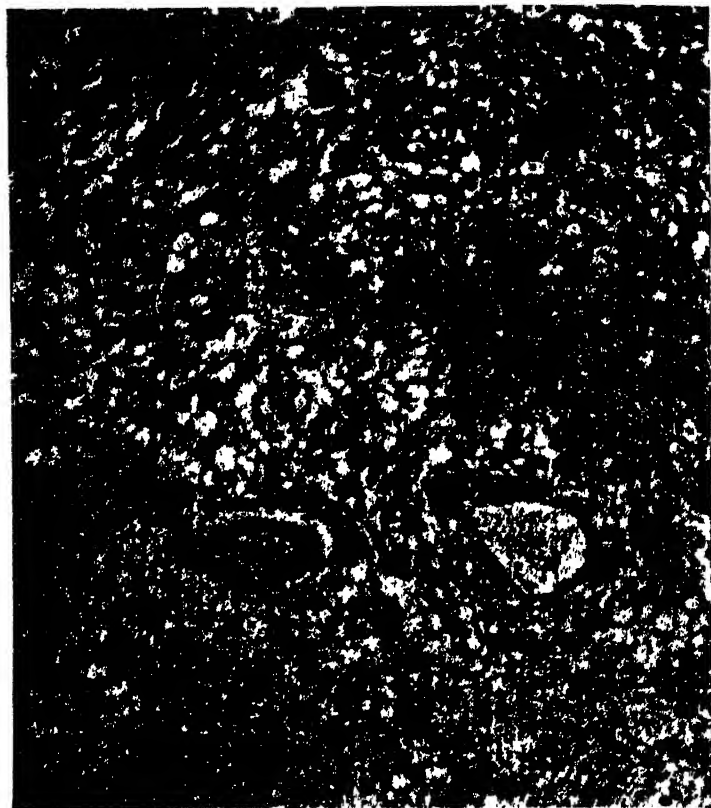


Fig. 319.—Astrocytoma. Note the uniformity of nuclei and the abundance of fibers.

normal structure, but with taller epithelium and numerous vacuoles containing mucus; (b) myxopapillary ependymoma, similar to above without mucus in the tumor cells but with abundant myxomatous degeneration in the stroma; (c) epithelial ependymoma, tumors composed of tubular channels resembling the central canal, with cells free of vacuoles and

mucus and often containing blepharoplasts; (d) cellular ependymoma, a highly cellular tumor containing fragments of tissue conforming to the other patterns, and often dotted with pseudo-rosettes. In these ependymomas, mitoses are uncommon. A more undifferentiated form, **ependymoblastoma**, occurs which grows rapidly and is highly malignant. **Colloid cyst** of the third ventricle may represent another form of ependymoma.

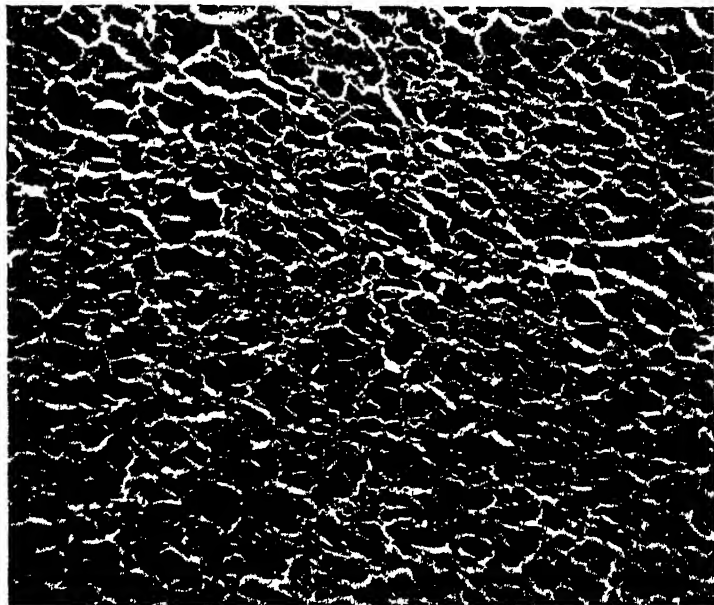


Fig. 320.—Gemistocytic astrocytoma.

2. **OLIGODENDROGLIOMA**.—Oligodendrogliomas grow very slowly and appear most commonly in the cerebral hemispheres of adults. The tumor often contains calcium (roentgenographically visible) and tends to become cystic. Histologically, they are extremely cellular and exhibit very little stroma. The nuclei are small, dark staining, and are surrounded by a halo of clear cytoplasm. Oligodendroblastomas are rare, highly malignant, rapidly growing variants of this tumor.

3. **ASTROCYTOMA**.—About one-half the gliomas, or one-fourth of all intracranial tumors, are astrocytomas. They

occur diffusely throughout the nervous system and are poorly demarcated grossly. They grow slowly and appear benign histologically. The cells are usually uniform, with nuclear structure comparable to that of a normal astrocyte. More cytoplasm is evident than in normal cells and stroma is densely fibrillated. Very often, gemistocytes are formed and occasionally dominate the histologic picture (gemistocytic astrocytoma). *Astroblastomas* are made up of larger cells with short thick vascular processes, often arranged in a radial pattern around a blood vessel. They exhibit more

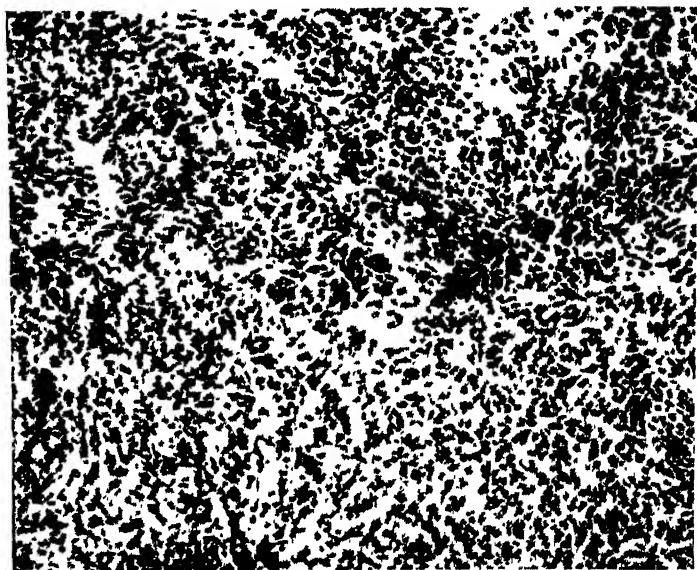


Fig. 321.—Medulloblastoma. Note the oval dark nuclei and the absence of fibers.

rapid growth. *Spongioblastomas* also may be considered a variety of astrocytoma.¹⁵ They are dominated, microscopically, by bipolar or unipolar cells which are thought to be the immediate stem cells from which astroblasts develop. Microscopically, they resemble neurofibromas. The cells and nuclei are regular in size and exhibit no mitoses. They grow slowly.

4. **MEDULLOBLASTOMA.**—Medulloblastomas comprise about 10 per cent of the gliomas and characteristically are rapidly growing midline cerebellar tumors of children. They spread

by implanting along the ventricles or in the meninges. Microscopically, the cells are small and pear-shaped, with a tapered cytoplasmic extremity. They tend to line up in incomplete circles, forming partial pseudorosettes. The tumor cells are radiosensitive, but the response to radiation is temporary.

5. **MEDULLOEPITHELIOMA.**—Medulloepitheliomas are rare, highly malignant tumors having a cellular structure which simulates the primitive medullary tube, the anlage of all structures of the central nervous system.

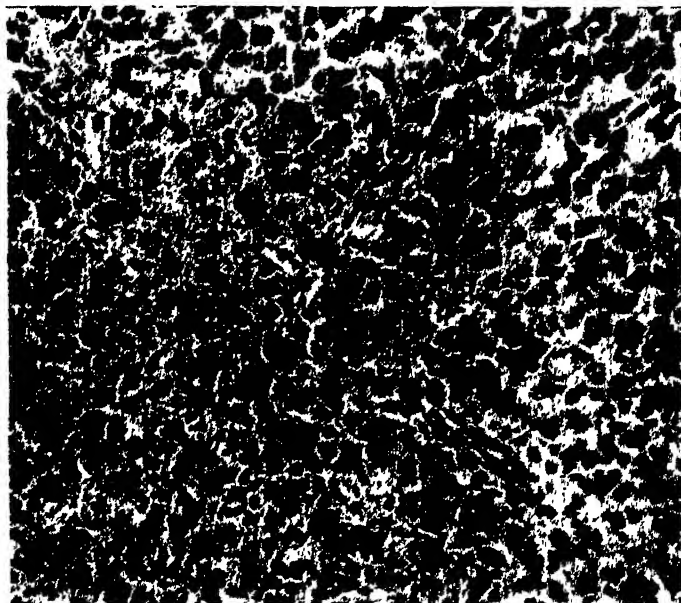


Fig. 322.—Glioblastoma multiforme.

6. **PINEALOMA.**—(See page 544.)

7. **GLIOBLASTOMA MULTIFORME.**—Glioblastoma multiforme is the second most common of the gliomas. The cellular source of these tumors is obscure. Microscopically, representatives of many stem cells can be identified, lending the variability of cellular form characteristic of the tumor. They are exceedingly malignant, rapidly expansive and invasive. They are often grossly hemorrhagic and their line of demarcation from cerebral tissue is indistinct. Microscopically, there is great variation in size and shape of cells, with giant and

multinucleate forms and numerous bizarre mitoses. There is frequently an endothelial hypertrophy and reduplication, imparting the appearance of extremely thick-walled vessels. Patches of necrosis surrounded by radiating clumps of small nuclei are very common.

8. **SYRINGOMYELIA**.—Syringomyelia is a cavitation occurring in the center of the spinal cord. It appears as a slowly progressive gliosis with subsequent cyst formation. The tumor may represent a variety of astrocytoma or may be formed by proliferation of ependymal processes. The cavity may be focal and round, fusiform and linear, or multiple. Its neoplastic character is questionable.

Neurocytomas.—The second group of primary intramedullary tumors consists of those stemming from the medulloblast in the direction of the nonsupporting element of the nervous system, the neurocyte.

1. **NEUROCYTOMA (GANGLIONEUROMA)**.—Neurocytomas are rare tumors characterized by the presence of mature nerve cells in which Nissl substance is demonstrable. They grow very slowly.

2. **NEUROBLASTOMA**.—Closely related to medulloblastomas, neuroblastomas are rare tumors composed of neuroblasts, identifiable by large vesicular nuclei in small rounded cells, with little cytoplasm and no Nissl substance. Neuroblasts can often be identified in medulloblastomas.

3. **RETINOBLASTOMA (NEUROEPITHELIOMA)**.—Occurring in childhood, retinoblastomas arise from the retinoblast, the representative of the neuroblast in the retina. Closely related to the medulloblastomas, they resemble them in behavior, implanting along meningeal spaces. They tend particularly to invade the optic nerve. Microscopically, the cells are small and round, with little cytoplasm, and tend to form rosettes (see Plate XV).

III. Extramedullary Neurogenic Tumors.—Neurogenic tumors developing outside the substance of the brain and spinal cord are tumors of peripheral ganglion cells and nerves, and of the stem cells of these structures. In addition, there are a number of neurogenic tumors arising in the adrenal medulla (see page 551), chromaffin structures (see page 461), and in the skin (melanoma, see page 634). Rarely, neurogenic tumors microscopically resembling neuroblastoma or medulloblastoma may be found in odd sites, such as bone, skin,

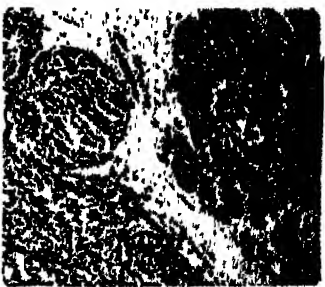
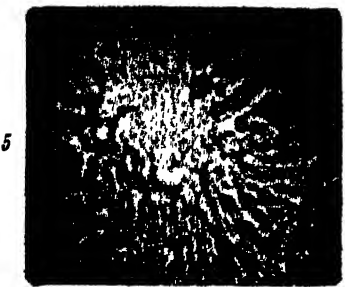


Plate XV.—Retinoblastoma: 1. Involvement of eye and optic nerve. 2. Tumor in eye. 3 and 4. Invasion of tumor over meningeal surface of brain. 5. Cross section of optic nerve, showing invasion by tumor. 6. Cerebral tissue invaded by tumor.

muscle, etc., where the stem cell is obscure but probably related to the migrant cell. The principal extramedullary primary neurogenic tumors are ganglioneuromas and neurofibromas.

1. **GANGLIONEUROMA.**—Ganglioneuromas are the peripheral counterpart of the central neurocytoma. Grossly, they appear as fleshy masses, often large, and are usually located along the thoracic and lumbar sympathetic trunk bulging into the mediastinum or retroperitoneal region. They grow slowly and are benign. Microscopically, they show mature nerve cells in a profuse stroma of sheath cells, fibrous tissue, and varying amounts of neurofibrils and myelin.

2. **NEUROFIBROMA.**—Three sources contribute to the morphology of the peripheral nerve: neuraxes of the nerve cells, sheath cells, and fibroblastic tissue from endoneural and perineural supporting structures. The contribution of neuraxes to the neurofibroma is insignificant. Tangles of neuraxes appear with their growth cones primarily in reparative processes (amputation neuroma). The relative importance of sheath cells (Schwannoma) or perineureum (perineuronal fibroblastoma) in the formation of neurofibromas is a much debated, and still unsettled, question. These tumors occur along peripheral nerves and at their endings. They may be single or multiple (see von Recklinghausen's disease, page 214), and they vary in diameter from one or two millimeters to several centimeters. They are encapsulated and are sometimes nodular. Microscopically, they are characterized by interlacing fiber bundles, palisading of nuclei, foam cells, and pigmented areas of degeneration. Very often, one or more of these findings may be absent. One particular variety of neurofibroma deserves special mention—the **acoustic neuroma**. This tumor arises from the sheaths of the eighth cranial nerve, usually within the internal auditory meatus. It extends inward, occupying the cerebello-pontine angle. Neurofibromas are slow-growing and benign.

IV. Tumors of Vascular and Perivascular Structures.—

1. **HEMANGIOMA.**—Hemangioma occurs most commonly over the surface of a cerebral hemisphere as a tangle of tortuous large and small vessels. Microscopically, it is similar to angiomas in other locations (see page 242).

2. **HEMANGIOENDOTHELIOMA.**—Hemangioendotheliomas are most common in the cerebellum of adults. They appear as a small firm reddish "mural nodule" in the wall of a large, smooth cyst. Histologically, they are composed of many im-

mature blood vessels with swollen endothelial lining cells. If associated with retinal angiomatosis the condition is called Lindau's disease.

3. **SARCOMA.**—Malignant, rapidly growing sarcomatous lesions occur in the brain, growing especially around blood vessels.

4. **LYMPHOBLASTOMA.**—Lymphoblastomatous tumors occur infrequently in the epidural space and within the substance of the brain or cord.

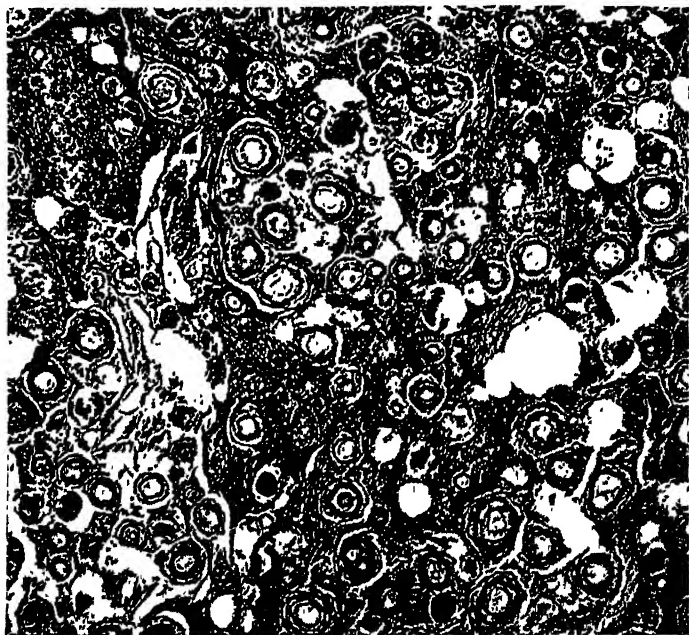


Fig. 323.—Meningioma. Very numerous rounded psammoma bodies are shown.

V. Tumors of the Meninges.—Meningiomas comprise about one-fifth of all intracranial neoplasms, being second only to gliomas in frequency. They are essentially benign tumors, which grow slowly, and compress the brain by expansion. The commonest sites are over the cerebral hemispheres, along the sagittal sinus, over the cribriform plate, and along the lesser wing of the sphenoid. They often erode the bone, and sometimes stimulate bone growth into the tumor. They are en-

capsulated, distinctly demarcated from brain tissue, and are always attached to meninges. The microscopic appearance varies greatly but is often highly cellular, with a pronounced whorled arrangement. The central portion of the whorls undergoes degeneration and calcification, forming psammoma bodies. The exact origin of the tumor is still debated, but that they arise from leptomeningeal cells is a common opinion. In rare instances a meningioma may not be localized but involves the brain surface over a wide area. Malignant fibrosarcomatous forms also occur.

VI. Mixed Tumors.—

1. EPIDERMOID TUMORS (pearly tumors, cholesteatomas), dermoid tumors, and teratomas. These tumors are thought to arise from congenital cell rests. Morphologically, they are similar to their counterparts elsewhere (see page 224).

VII. Hypophyseal Tumors.—These include the pituitary adenomas and craniopharyngiomas (see page 517).

VIII. Metastatic Tumors.—Metastatic tumors of the brain occur commonly from the lung, and somewhat less commonly from breast, stomach, kidney, adrenal, and prostate. Skin tumors involving the orbit sometimes invade the brain. Secondary tumors usually can be identified by their globular shape, sharp demarcation, and frequent multiplicity. Microscopically, they resemble the primary growth.

Developmental and Congenital Disorders

Related to faulty closure of the bony structures housing the medullary tube are numerous developmental disorders which vary primarily in degree of involvement. **Rachischisis** is a failure of formation of the dorsal arch throughout the length of the vertebral column, with exposure of the unclosed neural groove. **Myelocoele** is similar to rachischisis except that part of the dorsal arch (usually the thoracic portion) is formed. The spinal cord may be wholly or partially formed as a medullary tube. **Meningocoele** is a leptomeningeal protrusion through a local defect in bone and dura with the leptomeninges underlying the skin. This may occur in the vertebral column or skull. **Meningomyelocoele** is similar to meningocoele with the inclusion of spinal cord tissue in the protruding part. If brain is the part involved, the condition is called **encephalocoele**. **Syringomyelocoele** is similar to meningomyelocoele but with the addition of a marked distention of the central canal. **Spina bifida occulta** is a congenital local dorsal arch defect (usually lumbar or sacral),

in which the gap is filled with connective tissue to which the cord membranes are attached. With unequal growth of cord and vertebral column, tension of the cord results in neurological signs. This condition yields to surgical treatment.

Malformations may primarily involve brain tissue. **Anencephaly** is the condition wherein the forebrain and calvaria are absent. Often there are marked pathologic changes elsewhere, such as atrophy of adrenal glands. It probably is due to defective organization in primordial tissues. **Porencephaly** is an abnormal cavitation within the brain substance, the cavities usually communicating with the ventricles. The condition is looked upon as a partial agensia and is associated with maldevelopment elsewhere. **Heterotopias** are persistent islands of tissue which, though normal for certain developmental stages, are abnormal when found in the mature brain. Malformation of gyri is a common occurrence. Unusually large gyri are called **macrogyri**, unusually small ones, **microgyri**. Disturbances in brain volume are said to exist when brain weight in the adult varies beyond certain extremes. With an average weight around 1,350 grams, it is not uncommon to encounter brains weighing as little as 1,000 or as much as 1,700 grams. **Microcephaly** is the term applied to very small brains, **macrocephaly** to very large brains. Each condition is often associated with hydrocephalus. **Oxycephaly** is a condition in which a tower-shaped skull is associated with premature synostosis of cranial sutures. Mental deficiency, papilledema, and eventually blindness result from disproportionate growth of the brain in the deformed skull.

Congenital hydrocephalus is the condition of an abnormal amount of intracranial cerebrospinal fluid present at, or shortly after, the time of birth. Several descriptive terms are applied to the condition depending upon gross variations. **External hydrocephalus** describes the condition wherein most of the fluid accumulates over the surface of the brain. **Internal hydrocephalus** exists when the ventricular system is distended. **Hydromicrocephaly** refers to the condition of small head, early closure of fontanelles and sutures, with a concomitant hydrocephalus, usually both external and internal. Examples of this condition are the "pinheads" of circus fame. **Hydranencephaly** exists when the forebrain is represented only by a thin membranous sac filled with water. The head size may be normal and the fontanelles close appropriately. In **hydromacrocephaly** the head is enlarged, with fontanelles and sutures widely open.

The ventricular system is dilated, sometimes to a volume of several liters. Often the chambers are confluent. Considerable brain tissue often persists in the outer shell. These cases represent the condition most often referred to as hydrocephalus. **Communicating hydrocephalus** exists when abnormally increased fluid is present, although the connections between the ventricular system and the subarachnoid space are patent.

Theoretically, the production of hydrocephalus may be brought about in three ways: (1) by overproduction of fluid, (2) by obstruction to its flow, and (3) by interference with its absorption into the venous system.



Fig. 324.—Hydrocephalus. Note the extreme dilatation of ventricles, and the thinness of the cerebral substance. (Courtesy Dr. H. C. Schmeisser.)

The production of cerebrospinal fluid fluctuates with venous pressure. Hence, an obstruction to venous return from the choroid plexus might well cause excessive production of fluid. This situation may be found with tentorial tears in the newborn, where blood accumulates in the superior cistern and around the vein of Galen. Intracranial hemorrhage of this type is often associated with increased intracranial tension

and, at autopsy, an incipient hydrocephalus can be demonstrated. However, the extravasated blood and the resultant arachnoidal reaction may operate to obstruct the flow of fluid through the aperture of the tentorium cerebelli in the sub-arachnoid space. The condition would then represent an obstructive type of communicating hydrocephalus. Exuberant growth or cysts of choroid plexus are commonly found associated with infantile hydrocephalus, but probably are not causative.

Obstruction to the flow of cerebrospinal fluid is noted commonly in the following locations: (a) interventricular foramina (of Munro), (b) cerebral aqueduct (of Sylvius), (c) apertures of the fourth ventricle (of Magendie and Luschka), and (d) in the subarachnoid space at the constricted tentorial aperture. The etiology of the obstruction is often obscure, but there have been noted congenital atresia of the cerebral aqueduct, occluding tumors of the aqueduct in infants,¹⁶ and ependymitis with inflammatory changes producing obstruction, particularly at the interventricular foramina and aqueduct of Sylvius. Recently, toxoplasma has been incriminated as the inciting organism.¹⁷ The infection is thought to be transmitted in utero since the defect produced often can be allocated to early pregnancy by the stage of development of certain structures. Current opinion favors this as the most important single cause of congenital hydrocephalus (see page 169). Arachnitis from meningeal infection may obstruct cerebrospinal fluid flow by exuberant fibrous proliferations over the foramina of Luschka and Magendie and in the interpeduncular and superior cisterns at the tentorial aperture. This condition has been found in infants but is probably more important in generating adult hydrocephalus.

Interference with absorption of cerebrospinal fluid may occur from destruction of arachnoid granulations by meningitis. This mechanism of development of hydrocephalus also occurs in expanding central lesions of the brain which, by compressing the brain against the skull, obliterate the sub-arachnoid space over the vertex (see adult hydrocephalus, p. 719).

Other malformations of cerebral tissues include spastic diplegia, tuberous sclerosis, mongolism, and amaurotic family idiocy.

Spastic diplegia (Little's disease) is characterized clinically by spasticity of the lower extremities, choreiform movements, and sometimes, mental deficiency due to central neu-

ronal degeneration. Grossly, the brain is usually small and shrunken with patches of microgyri, and there may be gross defects in the cerebellum and pons. Although the inciting cause is thought to be a defect in development, it is possible that some diffuse active process as well may be at work to induce the symptomatology. The syndrome is duplicated in infantile encephalomyelitides and in toxic reactions. There is some evidence implying dissolution of the small internuncial cells in the spinal cord gray matter^{3, 18} imposing a block between cerebral influence and the final common path. Microscopically, the atrophied areas show gliosis.

Tuberous sclerosis is a congenital and familial disease manifest a few months to a few years after birth in mental deficiency, epileptiform seizures, cutaneous tumors similar to sebaceous adenomas, and often tumors of other organs. Grossly, the brain is small, firm, and dotted by areas of macrogyri, pearly white in color, and often nodular in form. Similar firm nodules may project into the ventricles. The nodules are composed of dense glial tissue and contain irregular giant cells and atypical glial elements. Hyperplasia of the sebaceous glands of the nose and cheeks (adenoma sebaceum) and benign embryonic tumors of the heart and kidneys are common accompaniments. The clinical syndrome characterized by mental changes and adenoma sebaceum of the skin in association with tuberous sclerosis of the brain is called *epiloia*.

Mongolian idiocy is characterized by mongoloid features in an idiotic child of Caucasian parents. The head is usually small, the tongue prominent, and the musculature hypotonic. The brain is small and there may be gross defects in the gyri. There is apparently a diminished number of cortical neurones, and the cortical architecture is distorted. Hypophyseal changes have been described (see page 520). The etiology is obscure.

Amaurotic family idiocy (Tay-Sacks disease) is a familial condition which occurs in infantile and juvenile forms. The infantile form is found mainly in the Jewish race. Progressive muscular weakness develops in the early months of life, and mental development fails. There is a characteristic peculiar cherry-red spot in the retina, and later optic atrophy and blindness develop. The brain is atrophic and firm. The cerebellum may share in the atrophy. The characteristic histologic feature is distention of many of the nerve cells by a granular deposit of lipid (lecithin) in the cytoplasm. The lipid deposit also involves cell processes. The degeneration of nerve cells and processes is followed by widespread gliosis.

The condition bears some relation to Niemann-Pick's disease, in which, likewise, lecithin may be found in nerve cells (see page 430).

In the juvenile form, which is more common in gentiles, the cherry-red spot in the macula is not present, and the lipoid in nerve cells is not lecithin, but stains well with the usual fat stains.

Demyelinating Diseases

The process of demyelination has been described as a secondary phenomenon following damage to continuity of nerve tissue (p. 681). A similar process is, however, observed frequently in the absence of any established primary cause.¹⁹ A group of diseases occurs characterized by demyelination, which may be patchy or diffuse.

Under the terms **diffuse leucoencephalopathy** is included a large, heterogenous group of diseases varying in age of appearance from infancy to adolescence, in onset from acute to gradual, and in course from a few months to many years. Familial or hereditary trends in some types are described. All are characterized by diffuse dissolution of white matter, usually bilateral and symmetrical, and beginning in the occipital lobes with extension forward. The terminus is often by aspiration pneumonia which interrupts the process at various stages. Grossly, the brain is soft and the white matter gelatinous or it may be sclerotic. Weigert stains show absence of myelin, with sparing of the short associational axones at the cortical margin. Older areas of degeneration show glial proliferation with formation of many bizarre cell forms and various areas of gliosis. Areas of active degeneration show a fat-granule cell reaction, with perivascular cuffing by fat-laden macrophages, and the meningeal spaces may contain large numbers of these cells. There may be diffuse sclerosis or none at all. References to this condition may be found under the terms diffuse sclerosis, leucoencephalopathy without sclerosis, progressive degenerative subcortical encephalopathy, encephalitis periaxialis diffusa, Schilder's disease, Krabbe's disease, and Pelizaeus-Merzbacher's disease.

Disseminated sclerosis (multiple sclerosis) is a relatively common disease of undetermined etiology, with onset usually between the ages of twenty and forty years. There are widespread scattered irregular lesions, predominantly in white matter, which appear grossly as yellow-gray areas on the cut surface of the brain or cord. These stand out prominently

as pale areas in Weigert preparations. They are most prominent in the long tracts of the cord, and lesions of the stem and cord figure conspicuously in the symptomatology. Microscopically, the lesion is a plaque of demyelination, and in degenerated areas of long standing there may be gliosis. The early degeneration appears to spare the axis cylinders, accounting for transient remissions. As in diffuse sclerosis, the microscopic picture depends on the duration of the lesion. In the active process fat-granule cells are operative, form perivascular cuffs, and spill into the subarachnoid space. The optic nerve is often involved. If the optic neuritis dominates and is associated with an acute patchy encephalomyelitis, the condition is called *ophthalmoneuromyelitis* (Devic's disease).

In subacute combined degeneration there is patchy degeneration affecting the posterior and lateral columns of the spinal cord. It is associated with macrocytic (pernicious) anemia and achlorhydria. The early lesions are focal areas of destruction of axis-cylinders and myelin sheaths, with softening and removal of degenerated material by microglial cells. Fusion of the areas and ascending and descending degeneration of cord tracts result in extensive damage of the posterior and lateral columns. Inflammatory reaction is absent, and little glial repair occurs. The damaged areas show only a delicate, spongy network of glial fibers. The exact relationship to pernicious anemia is still unknown. There is some evidence that early adequate liver treatment will prevent involvement of the nervous system. Since repair does not occur in the central nervous system, liver therapy will not undo the damage. Peripheral nerve demyelination is also common in pernicious anemia, and improvement in nervous symptoms following liver therapy is due mainly to repair of peripheral nerve degenerations.

Neuromuscular Disorders and Muscular Dystrophies

Dissolution of muscle may occur with pathologic involvement of the central nervous system, peripheral nerves, or muscles, and hence is conveniently described as myelopathic, neurotrophic, and myopathic.

MYELOPATHIC MUSCULAR ATROPHIES

Amyotonia congenita (Oppenheim's disease) has as its essential feature a paucity of cells in the anterior horn of the spinal cord. In a related condition (Werdnig-Hoffmann type) there is actual degeneration of the ganglion cells

and neuronophagia. There is weakness of muscles lacking their proper nerve supply, and microscopically the muscle fibers show marked variation in appearance, many being of embryonic type.

Friedreich's ataxia is one of a group of hereditary diseases in which ataxia is prominent. Degenerative changes occur in tracts of the spinal cord, so that the cord appears smaller than normal. Myelin sheath degeneration, particularly in the spinocerebellar and posterior columns, is shown by light unstained areas in Weigert preparations. The degeneration apparently begins in the cells of Clark's column. Late in the disease the pyramidal tracts may be involved. Gliosis follows the myelin degeneration.

Progressive muscular atrophy is a sporadic disease attacking young adults. The muscular atrophy may involve the upper extremity, or be bulbar or mesencephalic in position. Muscles lose their striations and diminish in size. Some normal fibers remain. The atrophy is secondary to degeneration of anterior horn cells. The disease is slowly progressive. There may be spontaneous stationary periods lasting for a number of years.

Amyotrophic lateral sclerosis is a disease appearing in later life and running a fairly rapid course to fatal termination. The pathologic changes are similar to those of progressive muscular atrophy with an added bilateral degeneration of the pyramidal tracts starting at the cerebral cortex.

NEUROTROPHIC MUSCULAR ATROPHY

Traumatic injury to a peripheral nerve results in muscular atrophy (see page 682).

Hypertrophic neuritis is a nodular proliferative condition of sheath cells along a peripheral nerve. There may be an associated central demyelination, particularly in the dorsal columns.

Peroneal muscular atrophy is a degeneration of the peroneal musculature with an associated proliferative neuritis. There is atrophy of the calf muscles, with foot drop and clubfoot. The disease is hereditary and occurs in the first decade.

MYOPATHIC MUSCULAR ATROPHY (DYSTROPHY)

Myasthenia gravis (see page 543).

Myotonia congenita is characterized by sustained contraction on voluntary movement. The muscles often are hypertrophied.

Progressive muscular dystrophy is a primary disease of muscles characterized by a prolonged course and great muscular weakness. The muscles may show a marked pseudohypertrophy. Microscopically, great variation in fiber size is apparent. Terminally, the muscle is replaced by connective tissue. Creatine appears in the urine.

Diseases of Extrapyramidal Motor System

In diseases of the extrapyramidal motor system, the lesions are localized or predominant in extrapyramidal parts known to affect motor activity. These parts include thalamus, basal nuclei (caudate, putamen, globus pallidus, claustrum, amygdaloid), and several lower stem nuclei (subthalamic body, nucleus ruber, substantia nigra). Clinically, there are disturbances in motor activity, manifested by tremor, choreiform movement, torsion spasm, or rigidity without true motor paralysis. The symptomatology varies with the topography of the lesion.

Progressive lenticular degeneration (Wilson's disease) is a familial condition appearing in an adolescent or young adult, its varying course progressing to a fatal ending in a few months to ten years. There is a bilateral symmetrical degeneration and cavitation of the putamen and, occasionally, the caudate nucleus. The involved tissue develops a spongy consistency. Microscopically, there is a marked glial proliferation, with the production of giant astrocytes. Associated with the disease in the basal nuclei there is a cirrhosis of the liver. In addition to the tremor and spasticity of skeletal muscles often there is striking emotional disturbance. A characteristic feature is the appearance of greenish pigmentation along the corneal margin (Kayser-Fleischer ring).

Pseudosclerosis (Westphal-Strümpell) occurs sporadically and in a younger age group (under 10) than Wilson's disease. The basal nuclei, with predominant thalamic involvement, are enlarged and sclerotic, but without a characteristic gross appearance. Microscopically, there is glial proliferation and gliosis. Cortical lesions may be present. The condition is often regarded as a form of Wilson's disease, which it resembles clinically.

Acute chorea (Sydenham's chorea) usually appears between the ages of 5 and 15 years. It is commonly associated with rheumatic fever, tonsillitis, exanthems, and various toxic and infectious encephalitides. There may be an associated rheumatic myocarditis. The cerebral lesions are difficult to

localize, but such striatal involvement as embolic softenings, focal degenerations, toxic changes in striatal cells, and even focal structures resembling Aschoff bodies have been described. Clinically, the disease is characterized by rapid, involuntary, purposeless movements and marked incoordination, especially of the upper extremity. Mentality is not affected. Recovery occurs in a few weeks to several years.

Chronic progressive chorea (Huntington's chorea) is a familial progressive disease appearing after 30 years of age. Sporadic cases are said to occur also. Profound mental changes are associated with the grimacing, gesticulation, and incoordination of the chorea. The corpus striatum is severely shrunken, with dissolution predominant among the smaller cells, and degeneration is found in the supragranular layers of the cerebral cortex. Secondary gliosis is present in lesions of long standing.

Paralysis agitans (Parkinson's disease, shaking palsy) is characterized clinically by coarse tremor (at rest) and muscular rigidity, most prominent in the upper extremity. Ordinarily the condition is progressive, with eventual appearance of the tremor in lower extremity, jaw and tongue, and marked alteration in gait. Two distinct forms, "essential" and "secondary," are recognized. Essential Parkinson's disease begins during or after the involutional period and progresses slowly. The secondary form is associated with epidemic encephalitis, cerebral trauma, and degenerations due to chemical poisoning (manganese, carbon monoxide). There are degenerative changes in the basal nuclei, which rarely may be evident grossly as lacunar softenings associated with vascular disease. Senile changes may accompany the essential form. Often the changes in the basal nuclei are evident only on quantitative study. Loss of nerve cells and nonspecific cellular changes (pigmentation, degeneration, swelling, and shrinkage) predominate. The substantia nigra is the principal site of involvement in postencephalitic parkinsonism, while the globus pallidus and putamen are damaged more prominently in the essential form.

Lesions of the basal nuclei may be associated also with *torsion spasm* (dystonia musculorum), a pattern of writhing distortions of the trunk; *spasmodic torticollis* (wryneck), a paroxysmal, jerky rotation of the head, often with eventual fixation; *athetosis*, purposeless writhing movements of the distal parts of extremities; *hemiballismus*, unilateral, wild flinging, exhaustive movements suggesting exaggerated chorea; and *myoclonus and tic*, twitchlike, rapid muscle movements.

The exact location of the lesions in these conditions is uncertain, and the symptoms are thought to arise from premotor cortical influence no longer modified by basal nuclear activity.

Diseases of Intracranial Vessels

Meningeal Vasculature.—The vascular system of the meninges includes three distinctive sets of vessels; the dural sinuses and their tributaries (emissary veins and superficial cerebral veins), the meningeal arteries, and the subarachnoid arteries. The dural sinuses and their tributaries are important in regard to both infections and hemorrhage, and the meningeal and subarachnoid arteries principally in relation to hemorrhage.

Sinus thrombosis is essentially a thrombophlebitis of a dural sinus. Cavernous sinus thrombosis is related to infections of the nose, upper lip, cheek, orbit, and sphenoid and posterior ethmoid paranasal sinuses. Superior sagittal sinus thrombosis occurs as a sequel to frontal sinusitis. Transverse sinus thrombosis is most often related to middle ear and mastoid infections. Superficial infections of scalp and neck and retropharyngeal abscesses can also give rise to sinus thrombosis by conduction along appropriate emissary veins. There is usually an associated leptomeningitis, and sinus thrombosis is thought to be important in the pathogenesis of some brain abscesses (see page 714).

Epidural hemorrhage ordinarily refers to blood in the temporal region from traumatic rupture of the middle meningeal artery or its branches, but rarely, is due to a tear of an emissary vein as it enters a dural sinus. This may be found in the posterior fossa from rupture of the mastoid emissary as it enters the transverse sinus. The hemorrhage is limited in extravasation to individual bone areas due to the dural attachments at the suture lines. The clot forming between dura and bone compresses the underlying brain tissue.

Dural or subdural hemorrhage (subdural hematoma, pachymeningitis hemorrhagica interna) occurs when bleeding from dural vessels extravasates in a subdural or intradural position forming a hematoma. Whether the hematoma is limited internally by a thin strip of dura or by false dural membrane is debatable. The bleeding point may be difficult to localize, but in recent traumatic cases can often be traced to the junction of superficial cerebral veins with dural sinuses. Usually there is a small amount of subarachnoid extravasation due to arachnoidal tears. The hematoma is most frequent over the frontal and parietal areas and is often bilateral. Al-

though generally regarded as traumatic, spontaneous cases have occurred in blood dyscrasias, infections, and toxemias. The hematoma organizes at its periphery, usually retaining a fluid center. Its clinical effects are due to the fact that it is a space-occupying mass.

Subarachnoid hemorrhage is from subarachnoid arteries which lie superficially in the subarachnoid spaces of the base of the brain and deep in the sulci over the other surfaces, or from subarachnoid veins which occupy a superficial position



Fig. 325.—Subarachnoid hemorrhage.

over the vertex. Bleeding from the latter vessels occurs as a result of trauma, blood dyscrasias, or rupture of a surface angioma. Blood may also appear in the subarachnoid space by rupture from a hemorrhage in brain tissue or by conduction with cerebrospinal fluid from an intraventricular hemorrhage. However, subarachnoid bleeding most commonly is from a ruptured aneurysm. The aneurysms are usually basal in position at points of vessel branching. The most important aneurysms are congenital or mycotic, but some have been ascribed to arteriosclerosis and syphilis.

"Congenital" aneurysms (see p. 239) are of fairly frequent occurrence. The angles of bifurcation of the arteries about the base of the brain are common sites. They are due to congenital weakness of the media at the point where the vessel branches.²⁰ The aneurysm itself is not always congenital, though the defect in the vascular wall is a congenital or developmental abnormality. Small leakages may occur through the wall of the sac, giving rise to pigmentation and thickening of meninges in the neighborhood of the aneurysm. Rupture of the aneurysm results in a subarachnoid hemorrhage, often rapidly fatal. The subarachnoid space about the region of the aneurysm (hence usually at the base of the brain) is found filled by recent blood clot. The clot may easily hide the aneurysm unless it is carefully removed. Occasionally the hemorrhage extends into the ventricles.

Mycotic aneurysms are produced by infected emboli lodging in cerebral vessels. Subacute bacterial endocarditis is the commonest source of the embolus, and the middle cerebral artery is the commonest site. Emboli bearing organisms of high virulence produce abscess or meningitis rather than mycotic aneurysm.

Birth injury may result from molding of the head during birth, which puts a strain upon the falx of the dura and the tentorium over the cerebellum. A tear may result sometimes with involvement of dural sinuses of the great cerebral vein (of Galen), and some subarachnoid hemorrhage may be found also.

Intramedullary Vascular Disease

Arteritis and vascular degeneration, with resulting thrombosis or hemorrhage, occurs as a result of vascular damage from many poisons (carbon monoxide, arsenic), in septic conditions (scarlet fever, pneumonia), blood dyscrasias (purpura, leukemia), periarteritis nodosa, Buerger's disease, and syphilis. The brain tissue shows multiple small hemorrhages or softenings. Syphilitic arteritis is probably the most important (see p. 238).

Arteriosclerosis.—Cerebral vessels are similar in structure to vessels elsewhere, though the small arteries contain a disproportionately large amount of connective tissue in their walls. With advance in age muscle decreases, the internal elastic lamina undergoes reduplication, and there is a medial fibrosis. Arteriosclerosis of the larger vessels at the base of the brain is of the atheromatous type. Through weakening

of the wall aneurysms may form. Cerebral arteriosclerosis may have no direct correlation with sclerotic changes elsewhere in the vascular system and has no constant relationship to hypertension. However, cerebral hyaline arteriolosclerosis is not uncommon with hypertension.⁴³ (See also, malignant hypertension, p. 711.) Narrowing of the vascular lumens diminishes the blood supply and exerts a serious effect on brain tissue. Multiple perivascular zones of atrophy may be found in the brain as a result of arteriosclerosis in addition to larger softenings from thrombosis. Particularly susceptible to diminished blood supply are the striatum, the hippocampus, dentate nucleus, and cerebral cortex. Degeneration of these areas plays a role in the pathogenesis of arteriosclerotic or senile cerebral atrophy. Arteriolar sclerosis also occurs in cerebral vessels and is characterized by the same hyaline changes seen in other organs.

Thrombosis develops in cerebral vessels from the same causes as elsewhere. A sclerotic vessel is usually involved and arteriosclerosis is the most frequent underlying cause of cerebral infarction. **Embolism** of cerebral arteries originates from thrombi in the lung, or more commonly, from the left side of the heart. Paradoxical embolism occurs from emboli breaking off in the right circulatory field and gaining access to the left side of the heart through an open foramen ovale. Air and fat also act as emboli (see p. 58). Massive infarction results most commonly from occlusion of branches of the middle cerebral artery, probably because this vessel is a direct continuation of the internal carotid artery. Consequently, the middle cerebral artery is in direct line for receiving emboli, as well as being subject to the wear and tear of direct pressure effects from the heart.

Occlusion of a cerebral artery results in infarction of the region supplied by the vessel. Even though abundant anastomoses are present, they are insufficient to maintain nutrition if an artery is blocked; i.e., functionally they are end-arteries. Cerebral infarcts are characterized by softening. The clinical effects depend upon the area of nervous tissue involved. The appearance of a cerebral infarct depends upon its age. A recent infarct may be indistinguishable in a fresh brain, but after fixation it remains soft in comparison with surrounding tissue. If its age is greater than two or three days, it appears as a soft, semi-fluid area, with a slightly yellowish color and an edematous, sometimes hemorrhagic, edge. Later, when the necrotic and liquefied material has been removed, the region is shrunken and depressed. If the

infarcted area is large, it may have a cystlike center containing yellowish fluid (apoplectic cyst) encapsulated by glial tissue.

Microscopically, a very recent infarct transiently contains neutrophilic leucocytes, but they soon disappear. Nerve cells, axis cylinders, and neuroglial cells degenerate, and lipoid of the myelin sheath is broken down and liquefied. The fatty and necrotic material undergoes phagocytosis and is removed by the ameboid microglial cells. These scavengers appear abundantly as rounded cells with a foamy or vacuolated cytoplasm (fat-granule cells, compound granular corpuscles). Healing occurs by proliferation of a granulation tissue composed of astrocytes, capillaries, and a few fibroblasts of the adventitia of adjacent vessels. Eventually a dense neuroglial scar is formed. The damage is permanent, as there is no regeneration of the injured nerve cells and fibers.

Cerebral Hemorrhage.—Hemorrhages into the brain tissue itself may be either small petechial or perivascular hemorrhages, or a massive hematoma. Small petechial hemorrhages result from many types of relatively minor trauma, and if numerous or repeated may give rise to mental changes, e.g., the "punch-drunk" condition of old pugilists. Petechial hemorrhages also may result from poisons, such as carbon monoxide and arsphenamine, or from purpuric or leucemic conditions. Massive intracerebral hemorrhage is due to vascular disease, with or without high blood pressure. It is a frequent end result of hypertensive cardiovascular-renal disease. The vessels most commonly affected are the lenticulostriate branches of the middle cerebral artery, involving the basal ganglia and internal capsule. Less frequently there is hemorrhage into the white matter of the cerebrum, or into the pons or cerebellum. The actual mechanism of the hemorrhage is debatable, and it is usually impossible to find the point of vascular rupture. The brain bulges slightly on the side of the hemorrhage, where there is some flattening of the convolutions. Cutting through the brain tissue reveals the area of hemorrhage lacerating the brain substance. Rupture into a ventricle often occurs, and in such cases blood appears in the spinal fluid. Hemorrhage into cerebral tumor tissue may be grossly indistinguishable from the ordinary type of cerebral hemorrhage. Microscopic examination is necessary to confirm or rule out this possibility.

Brain in Malignant Hypertension.—In malignant hypertension the brain may be edematous or sclerotic. Arteriolar changes, hyaline or vacuolar, usually occur, with narrowing

of the lumens. The ratio of thickness of vessel wall to diameter of the lumen may be altered from the normal of 1:3.5 to as much as 1:1.7.²¹ Hemorrhages varying from petechial to massive size may be found, and areas of infarction, usually multiple and small but sometimes massive. Sometimes there is edema, slight perivascular lymphocytic infiltration, and gliosis (see p. 293).

Degenerative Encephalopathies

Various degenerative lesions of the nervous system are due to soluble toxins, chemical poisons, anesthesia, uremia, diabetic coma, hypoglycemia, metrazol and shock therapy, and deficiency diseases.

The group due to soluble toxins includes: tetanus, botulism, and a heterogeneous group of undetermined etiology referred to as "toxic" encephalopathy. **Tetanus** (see p. 73) exerts its effect by its neurotropic toxin. Morphologic changes in the nervous system are not striking although there are hyperemia, swelling of nerve cells, and failure of staining of synaptic structures. **Toxic encephalopathy** is the term which may be applied to many conditions having symptoms of encephalitis, and sometimes occurring in measles, mumps, pneumonia, typhoid fever, scarlet fever, erysipelas, and other streptococcic infections, and pertussis. The gross pathologic changes of hyperemia, edema, and petechial hemorrhages are nonspecific. Microscopically, the tissues are free of neutrophilic infiltration but may show satellitosis, nerve cell body changes including swelling, chromatolysis and nuclear damage, and vascular responses such as hemorrhages and endothelial proliferation. **Chemical poisons**, such as arsenic, lead, manganese, carbon monoxide, and alcohol, may give rise to degenerative changes in the nervous system. The mechanism is ascribed to actual toxic necrosis implicating vascular structures primarily, or to relative or absolute anoxia. Pathologic alterations include edema, congestion, focal softenings, and hemorrhages. Actual inflammatory changes are rare. The changes being nonspecific, demonstration of the toxic substance is essential to diagnosis. **Anesthetic agents** such as ether, chloroform, nitrous oxide, cyclopropane, and barbiturates have all been incriminated as occasional causes of death. Relative anoxia usually is described as the mechanism by which neuronal degeneration is induced. The cerebral changes produced by **anoxia** (e.g. as in high altitude flying), circulatory arrest, carbon monoxide poisoning, hypoglycemia and anesthetic agents are all very

much alike, apparently influenced by both vascular and metabolic factors.³¹ Similar anoxic changes are found in fatalities following fever therapy.³² Ether and chloroform, as strong fat solvents, have been known to precipitate demyelination and are generally regarded as dangerous in any patient with a demyelinating disease. Microscopically, there may be found satellitosis, glial proliferation with the formation of glial nodes, and nonspecific changes in the nerve cell bodies, such as shrinkage and nuclear pyknosis. **Uremia** may be accompanied by marked edema of the brain, with pressure marks and coning, and anemia, believed due to the swelling of the brain. The nerve cells are swollen and sometimes there is perivascular cuffing. The pathogenesis is obscure. **Diabetic coma** is usually accompanied by little morphologic change. It is usually considered due to relative anoxia, rather than toxemia. **Hypoglycemia** due to insulin therapy or a tumor of pancreatic islet tissue may exhibit cerebral signs. Changes in the nervous system include chromatolytic, vacuolar, and pyknotic nerve cell alterations (nonspecific), formation of pseudogiant cells, gemistocytosis, degeneration of axis cylinders, and petechial hemorrhages.²² **Metrazol and shock therapy** may produce cerebral brain damage similar to that of hypoglycemia. Hemorrhage may be prominent, particularly in electric therapy. **Vitamin deficiency diseases** particularly pellagra, beriberi, rickets, and scurvy may have associated nonspecific degenerative changes in the nervous system (see p. 192).

Encephalitis

Inflammatory diseases of the central nervous system may be due to parasitic and fungus infections, syphilis, bacterial infections, rickettsial diseases, and virus diseases.

Parasitic and fungus infections include toxoplasma, trichina, pork tapeworm (cysticercosis), malaria, and actinomycosis (see Chap. VIII). *Torula* (cryptococcus) affects both meninges and brain (see page 158). *Syphilis* frequently involves the central nervous system (see page 140).

Bacterial infection of the central nervous system may produce suppurative encephalitis or brain abscess. Staphylococci are the most common organisms, although streptococci, pneumococci, and others may be causative. Cultures at autopsy often yield mixed agents. The organism may be introduced by direct implantation (trauma, surgery), contiguous extension (e.g., from erosion of bone and dura over an otitis media), or metastatic extension (e.g., from bron-

chiectasis). A centrally located abscess sometimes has no identifiable primary focus, although it is assumed that all are secondary to some other focus of infection, which is presumed to have disappeared while the brain abscess was developing. Lesions with which brain abscess is commonly associated include otitis media, sinus thrombosis, bronchiectasis, empyema, lung abscess, and bacterial endocarditis.

Brain abscesses occur most commonly in the temporal lobe and cerebellar hemispheres. If embolic they are usually multiple. Grossly, the abscess is encapsulated and has a fluid purulent center. The developing abscess goes through the stages of focal necrosis, invasion by leucocytes, liquefaction and formation of pus, fat-granule cell reaction, peripheral fibrinous precipitate, surrounding hyperemia and fibroblastic proliferation, and mild marginal gliosis.¹⁸ The fully formed abscess thus has four microscopic layers from within out: (1) a central necrotic core, (2) a vascular granulomatous border, (3) a zone of hyperemia and fibrosis, and (4) an external zone of gliosis. Spontaneous resolution of a cerebral abscess probably does not occur. Rupture of an abscess results in disseminated suppurative encephalitis and purulent meningitis.

Various *viral* and *rickettsial* infections produce encephalitis (see Chap. VI).

Meningitis

Pachymeningitis.—Inflammation of the dura may develop by spread from overlying bone. Hence it may complicate osteomyelitis of the skull, compound fracture, etc. The dura tends to localize the lesion with the production of an **epidural abscess**. The overlying area of the scalp is swollen, congested, and edematous (Pott's puffy tumor). **Subdural abscess** may occur secondary to neighboring infections. This consists of a broad limited sheet of purulent material or organized exudate. **Peripachymeningitis** is an inflammatory condition associated with Pott's disease (see page 657). **Pachymeningitis cervicalis hypertrophica** is a pronounced thickening of the dura in the cervical region which may be associated with syphilis.

Leptomeningitis.—Inflammations of the leptomeninx may be purulent, due to bacterial and actinomycotic infections, or nonpurulent, due to tuberculous, syphilitic, lymphocytic, and torula meningitis.

Purulent meningitis may be caused by meningococci, pneumococci, streptococci, staphylococci, gonococci, influenza

bacilli, actinomyces, and rarely, colon bacilli in infants. The most important of these is the meningococcus, which gives rise to the epidemic form of meningitis as well as occasional sporadic cases. In meningococcus meningitis the organism is believed to reach the meninges by passage through the nasopharynx, where it leaves no trace, and then along the perineural sheath of the olfactory nerve, through the cribriform



Fig. 326.—Streptococcal meningitis. An abundant purulent exudate can be seen covering the base of the brain. (Courtesy Dr. H. C. Schmeisser.)

plate of the ethmoid, to reach the meninges. Another possible route of meningeal infection is by blood stream. Acute fulminating forms of meningococcal infection are septicemic and systemic, with hemorrhagic spots in the skin (hence the term "spotted fever"). The purulent exudate is most abundant over the base of the brain, and extension commonly occurs to the spinal meninges. The infection usually spreads to the choroid plexus and the interior of the ventricles. Some degree of acute internal hydrocephalus results from increased



Fig. 327.—Acute meningitis. Note the involvement of blood vessels.

permeability of the choroid plexus, outpouring of exudate into the ventricles, and interference with outflow due to inflammatory swelling about the narrow ventricular openings. This, along with the edema, congestion of blood vessels, and subarachnoid exudate, increases the intracranial pressure.

The other purulent meningitides resemble the meningococcic form both grossly and microscopically, necessitating identification of the organism for diagnosis. Streptococcic

and pneumococcic exudates appear most abundantly over the vertex, whereas meningococcic exudate tends to aggregate at the base. In meningitis due to the influenza bacillus, the exudate is most abundant and diffuse.

Nonpurulent meningitis may be a tuberculous meningitis, secondary to a tuberculous lesion elsewhere and often but part of a generalized miliary tuberculosis. In other cases it is the most prominent active focus of tuberculosis in the body. It is almost invariably fatal. The brain is swollen, and a gelatinous, translucent, slightly greenish exudate may be evident in the subarachnoid space. If exudate is abundant, it usually involves the base of the brain and spreads through the sylvian cisterns. Tiny opaque yellowish flecks which represent minute tubercles are evident along the course of subarachnoid vessels or on the choroid plexus. Microscopically, the inflammatory reaction and exudate are in general similar to tuberculosis elsewhere, but tend to show more neutrophilic leucocytes. The predominant cells, however, are large mononuclears, lymphocytes, plasma cells, and epithelioid cells. Small areas of caseation and definite tubercles may be found. Giant cells are not numerous. The inflammatory process often involves the superficial portions of the cortex, so that the condition is really a meningo-encephalitis.²⁵ Blood vessels passing through the exudate show adventitial inflammation, and intimal thickening (tuberculous arteritis). Fibroblastic proliferation causes a meningeal thickening. Tubercles may be found involving choroid plexus and ependyma.

The pathogenesis of tuberculous meningitis is a matter of dispute. The three main theories are: (1) hematogenous infection of the cerebrospinal fluid, (2) hematogenous spread to choroid plexus, with development there of a tubercle which later infects leptomeninges, and (3) hematogenous spread to superficial cerebral cortex, with development of a localized tubercle, which later ruptures or spreads infection to meninges. Rich and McCordock²⁴ demonstrated this last type of origin in a large proportion of their cases.

Tuberculoma of the brain is a large solitary tuberculous lesion in the cerebral or cerebellar cortex. Its symptomatology may cause confusion with a neoplasm. The microscopic structure is similar to that of tuberculous lesions elsewhere.

Lymphocytic choriomeningitis, believed to be caused by a virus, has a transitory, nonfatal course. There is marked

lymphocytic infiltration of the subarachnoid spaces with appearance of large numbers of lymphocytes in the cerebrospinal fluid (see p. 114).

Torula meningitis is a chronic meningeal irritation by a fungus, *Cryptococcus hominis* (see page 158).

Syphilitic meningitis (see page 139).

Diseases of Peripheral Nerves

The diseases of peripheral nerves fall into the three ill-defined categories of neuralgia, neuritis, and traumatic injury. The changes resulting from peripheral nerve trauma are those of Wallerian degeneration and neuroma formation (see page 682).

Neuralgia refers to pain in the distribution of a nerve supply, the principal ones being trigeminal and sciatic. The character of the pain is distinctive, being intermittent or remittent and very severe. Morphologic changes in the involved peripheral nerve are absent or negligible. Changes in ganglia are sometimes described, such as chromatolysis and shrinkage, but it is difficult to ascribe the symptoms to these nonspecific alterations. The pain has been attributed to peripheral nerve or nerve ending involvement, reflex vasospasm, possibly related to histamine hypersensitivity, and to heightened central synaptic activity which accentuates above the pain threshold the normal afferent impulses from a region.

Neuritis is a term used loosely in referring to any condition associated with inflammatory or degenerative changes in peripheral nerves. When many nerves are involved the condition is described as **polyneuritis**, if one nerve as **mononeuritis**. Various changes which may be found include hyperemia of the nerve sheath, transudation and swelling, cellular exudate, myelin degeneration, and swelling and fragmentation of axis cylinders. Once continuity of fibers is broken, secondary Wallerian degeneration occurs. From an etiologic standpoint, Cobb and Coggeshall²⁸ have grouped the neuritides under the following headings: (1) virus (herpes), (2) bacteriotoxic (scarlet fever), (3) deficiency or metabolic (beriberi), (4) chemical (lead), (5) focal mechanical (tumor pressure), (6) focal infectious (diphtheria). A large number of etiologic agents operate in each category.

Intracranial Tension

The relative rigidity of the cranial vault leads to increased intracranial tension from changes in volume of its contents.

For this reason space-occupying lesions, conditions limiting the flow of cerebrospinal fluid, and edema of the brain give rise to an elevated intracranial pressure. This brings about certain pathologic changes of great clinical importance.

Changes in Extramedullary Fluid Volume (see also p. 698).—In the adult, hydrocephalus occurs in a number of chronic diseases as a moderate dilatation of the ventricular system often along with a slight external hydrocephalus (distended subarachnoid space). This may be seen in syphilis, chronic alcoholism, and chronic subarachnoid obstructions such as after meningitis. Very often the mechanism is obscure. In syphilis, involvement of the arachnoid villi may inhibit absorption of fluid. In chronic alcoholism, successive bouts of edema of the brain may be postulated with subsequent distention of the ventricles and contraction of brain tissue by atrophy. In addition, an ependymitis with nodular subependymal gliosis and profuse vascular endothelial proliferation may be noted in alcoholism, which may cause transitory obstruction to cerebrospinal fluid flow during bouts of edema. The mechanism of obstruction due to arachnoidal thickening is less obscure. In addition to thickening following meningitis, chronic arachnitis has been observed after repeated subarachnoid hemorrhage (seeping aneurysm). At autopsy, such brains usually exhibit a moderate internal hydrocephalus. In cerebral atrophy, associated with senility, there is often a marked external hydrocephalus. The absence of ventricular dilatation in such cases indicates that pressure phenomena had little to do with the accumulation of fluid over the atrophied brain. A more acute ventricular distention in the adult occurs in purulent meningitis and with intraventricular block.

Changes in Intracranial Tissue Volume.—Changes in tissue volume within the cranium may be brought about by (1) accumulation of intramedullary (interstitial) fluid (edema), (2) increase in vascular volume (congestion), and (3) new tissue growth (tumor). In these conditions hydrocephalus is absent. The subarachnoid space often is obliterated and the surface of the brain is dry. Underlying gyri are compressed and markedly flattened and the sulci are obscured. The opposing walls of the ventricles may be in apposition. A distinctive characteristic is the appearance of pressure marks along the base of the brain. The cerebellar tonsils may be shoved over the brim of the foramen magnum, grooving the cerebellum deeply (coning). In addition, the swollen temporal lobes may spread over the free margins of

the tentorial aperture with a consequent linear grooving on their medial surfaces. Edema may be related to cardiac decompensation, generalized septic and toxic states, and cachexia. Microscopically the brain tissue is vacuolated, the cells appearing widely separated. Congestion occurs in many inflammatory conditions as well as in cardiac failure and polycythemia. With congestion alone, increase in total tissue volume is usually not excessive, as shown by absence of pressure marks.

Papilledema.—Papilledema or choked disc is an important clinical index of increased intracranial pressure, as it may be visualized directly by an ophthalmoscope. Grossly, there is venous distention with surrounding edema, congestion, and elevation of the disc. There may be small hemorrhages in and around the papilla. If unrelieved, secondary optic atrophy follows. Microscopically, there are distention of the central vein, lateral shift of the retina, forward bulge of the anterior component of the lamina cribrosa, and distortion of the fibers entering the nerve head. The development of papilledema depends upon two factors. (1) The vaginal spaces of the optic nerve convey the interstitial fluid of the bulb into the subarachnoid space at the base of the brain. (2) The venous drainage of the posterior retina is through the central vein which drains into the ophthalmic and thence to the cavernous sinus. The central vein bridges the vaginal spaces of the optic nerve in passing from a central position within the nerve to the ophthalmic vein. Pressure obstruction of this vein produces congestion at the papilla, and edema follows obstruction of drainage through the vaginal sheath. Diapedesis from the obstructed vein produces the small hemorrhages at the nerve head, and transudate contributes to the edema. The relative importance of the two mechanisms is not known, and usually, both appear to be in operation. Experimentally, obstruction of the subarachnoid space alone does not induce severe choked disc. The most severe papilledema is induced by hemorrhage invading the optic sheath and, by distention of the space, obstructing the venous return through distortion of the central vein, an event which may be brought about by a ruptured basal aneurysm. In this condition, massive intraretinal hemorrhages sometimes occur.²⁷

Epilepsy and Major Psychoses

Epilepsy.—In the idiopathic or “essential” forms of epilepsy, morphologic changes include only nonspecific alterations in brain tissue, the significance of which may be

seriously questioned. Biochemical and electrophysiologic studies have contributed greatly to an understanding of the operative mechanisms. In the secondary form, the convulsive states are associated with pathologic changes in the nervous system. The pathogenesis is often clearly indicated and the symptom may be related to an inflammatory, circulatory, space-occupying, or degenerative lesion.

Major Psychoses.—The "functional" psychoses are so described because of the absence of demonstrable structural changes in the nervous system, and because the functional changes occurring are presumed to be psychogenic in origin. A number of nonspecific nerve cell and glial alterations have been described as occurring regularly in these conditions. There is no general agreement as to whether these changes precede or follow the abnormal psychic state.

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